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Severe falciparum malaria

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Child with severe falciparum malaria in rural Myanmar (copyright © D. A. Warrell).

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SEVERE FALCIPARUM MALARIA
[*Severe and Complicated Malaria*, third edition]

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Severe falciparum malaria

World Health Organization, Communicable Diseases Cluster, 1211 Geneva 27, Switzerland

Introduction

The current knowledge of severe malaria was reviewed at informal technical meetings convened by the World Health Organization (WHO) in Kuala Lumpur, Malaysia in 1985 and in Geneva, Switzerland in 1988.

These meetings resulted in the publication of two editions of *Severe and Complicated Malaria (Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 80, supplement, 1986, and vol. 84, supplement 2, 1990 [also translated into French]), a publication entitled *Management of Severe and Complicated Malaria, A Practical Handbook* (Geneva: WHO, 1991), the development of guidelines for health care workers in tropical Africa in 1992, and a training module for medical and nursing professionals.

A further meeting, sponsored by WHO, was held on 4–8 December 1995 in Geneva. The purpose was to review in great detail the latest scientific evidence for, and practical experience in, the clinical management of severe malaria in children, adults and pregnant women. This present publication is based on that meeting and subsequent discussion and correspondence with leaders in this field.

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Definition of severe falciparum malaria

Almost all of the estimated >1 million deaths from malaria each year world-wide are attributable to *Plasmodium falciparum*.

Any patient with malaria who is unable to swallow tablets, has any evidence of vital organ dysfunction, or a high parasite count is at increased risk of dying. The exact risk depends on the degree of abnormality, age, background immunity, and access to appropriate treatment. A strict definition of severe malaria has been included in this and previous editions to assist clinical and epidemiological descriptions. In clinical practice the patient must be assessed and treated immediately. The parasite count, haematocrit, haemoglobin and blood glucose levels may all be available immediately, but other laboratory indices will take time to obtain, and treatment should not depend on fulfilling these criteria, or waiting for all laboratory results to be available. As severe malaria is a potentially fatal but treatable disease, any patient considered at increased risk should be given the benefit of the highest level of care available.

The purpose of attempting to define and describe severe falciparum malaria is twofold. First, to alert clinicians and other health care workers to the symptoms and signs which are associated with progression to life-threatening disease. Second, to indicate the clinical features which should be looked for and systematically recorded in any research study of severe falciparum malaria.

The appropriateness of any definition will vary with the use to which it is to be put, the facilities available and the clinical spectrum of disease in any given environment. Thus a definition that seeks to measure the clinical load on a health service needs to be broad and inclusive whereas a definition used to identify groups for studies of pathogenesis needs to be precise and exclusive in order to achieve homogeneity.

Despite these difficulties, and accepting that definitions are always likely to be controversial, we consider it appropriate, useful and thought provoking to attempt to define and to describe what is generally meant by severe falciparum malaria.

Those at risk

In parts of the world where endemicity of falciparum malaria is stable, severe malaria is mainly a disease of children from the first few months of life to the age of 5 years. It is less common in older children and adults, because of the acquisition of partial immunity. In areas of lower endemicity, severe malaria occurs in both adults and children. Non-immune travellers and migrant workers are also vulnerable to severe malaria. There are important differences in the clinical spectrum of severe malaria with age. In the following sections the same basic definition of severe disease is used and the accompanying notes specify differences between children and adults.

Severe manifestations of P. falciparum *malaria*

In a patient with *P. falciparum* asexual parasitaemia

Table 1. Severe manifestations of *P. falciparum* malaria in adults and children[a]

Prognostic value[b] Children	Prognostic value[b] Adults	Clinical manifestations or laboratory finding	Frequency[b] Children	Frequency[b] Adults
+	(?)[c]	Prostration	+++	+++
+++	++	Impaired consciousness	+++	++
+++	+++	Respiratory distress (acidotic breathing)	+++	+
+	++	Multiple convulsions	+++	+
+++	+++	Circulatory collapse	+	+
+++	+++	Pulmonary oedema (radiological)	+/–	+
+++	++	Abnormal bleeding	+/–	+
++	+	Jaundice	+	+++
+	+	Haemoglobinuria	+/–	+
+	+	Severe anaemia	+++	+

[a]See the section on severe malaria in children.
[b]On a scale from + to +++; +/– indicates infrequent occurrence.
[c]Data not available.

Table 2. Outline classification of severe malaria in children

Group 1
Children at immediately increased risk of dying who require parenteral antimalarial drugs and supportive therapy
(a) Prostrated children (prostration is the inability to sit upright in a child normally able to do so, or to drink in the case of children too young to sit)
Three subgroups of increasing severity should be distinguished
(i) Prostrate but fully conscious
(ii) Prostrate with impaired consciousness but not in deep coma
(iii) Coma (the inability to localize a painful stimulus) (refer to Table 3)
(b) Respiratory distress (acidotic breathing)
(i) Mild—sustained nasal flaring and/or mild intercostal indrawing (recession)
(ii) Severe—the presence of either marked indrawing (recession) of the bony structure of the lower chest wall or deep (acidotic) breathing
Group 2
Children who, though able to be treated with oral antimalarial drugs require supervised management because of the risk of clinical deterioration but who show none of the features of group 1 (above)
(a) Children with a haemoglobin level <5 g/dL or a haematocrit <15%
(b) Children with 2 or more convulsions within a 24 h period
Group 3
Children who require parenteral treatment because of persistent vomiting but who lack any specific clinical or laboratory features of groups 1 or 2 (above)

and no other confirmed cause for their symptoms the presence of one or more of the clinical or laboratory features in Table 1 classifies that patient as suffering from severe malaria.

Many of the elements in Tables 1 are not independent; it is not always clear which have the strongest prognostic significance and not all can be recorded with equal ease. For example, metabolic acidosis plays a major role in the pathogenesis of severe malaria but few hospitals can measure acid–base status. However, some are able to measure lactate and all can record the presence of respiratory distress or deep breathing, which have excellent sensitivity and specificity for detecting acidosis (ENGLISH *et al.*, 1996a).

A classification of severe falciparum malaria in children

Over 90% of all cases of life-threatening malaria are in African children. In many places the resources for systematic detection and recording of the elements in Table 1 are lacking.

A classification based on both need for treatment and prognosis is given in Table 2. It is particularly suitable for descriptive studies of the burden on health facilities, for epidemiological surveillance of severe disease and for the rapid identification of children needing either referral or increased attention once referred. When a more precise definition is required, Table 2 should be used in conjunction with Table 1. Less information is available on the clinical spectrum of severe malaria in children outside Africa but we believe that the outline classification in Table 2 can usefully be extended to this group.

Table 3. A coma scale for children (Blantyre coma scale)[a]

	Score[b]
(a) **Best motor response**	
Localizes painful stimulus[c]	2
Withdraws limb from pain[d]	1
Non-specific or absent response	0
(b) **Verbal response**	
Appropriate cry	2
Moan or inappropriate cry	1
None	
(c) **Eye movements**	
Directed (e.g., follows mother's face)[e]	1
Not directed	0

[a]This coma scale (MOLYNEUX *et al.*, 1989a) is modified from the widely used Glasgow coma scale (TEASDALE & JENNETT, 1974) to be applicable to children, including those who have not learned to speak.
[b]Total score can range from 0 to 5; 2 or less indicates 'unrousable coma'.
[c]Painful stimulus: rub knuckles on patient's sternum (Fig. 2a)
[d]Painful stimulus: firm pressure on thumbnail bed with horizontal pencil (Fig. 2b).
[e]See Fig. 3.

The following notes provide further information on the clinical and laboratory observations in Tables 1 and 2.

Prostration. This is the inability to sit unassisted in a child who is normally able to do so. In children not old enough to sit up it is defined as the inability to feed. Prostration must always be recorded directly and not

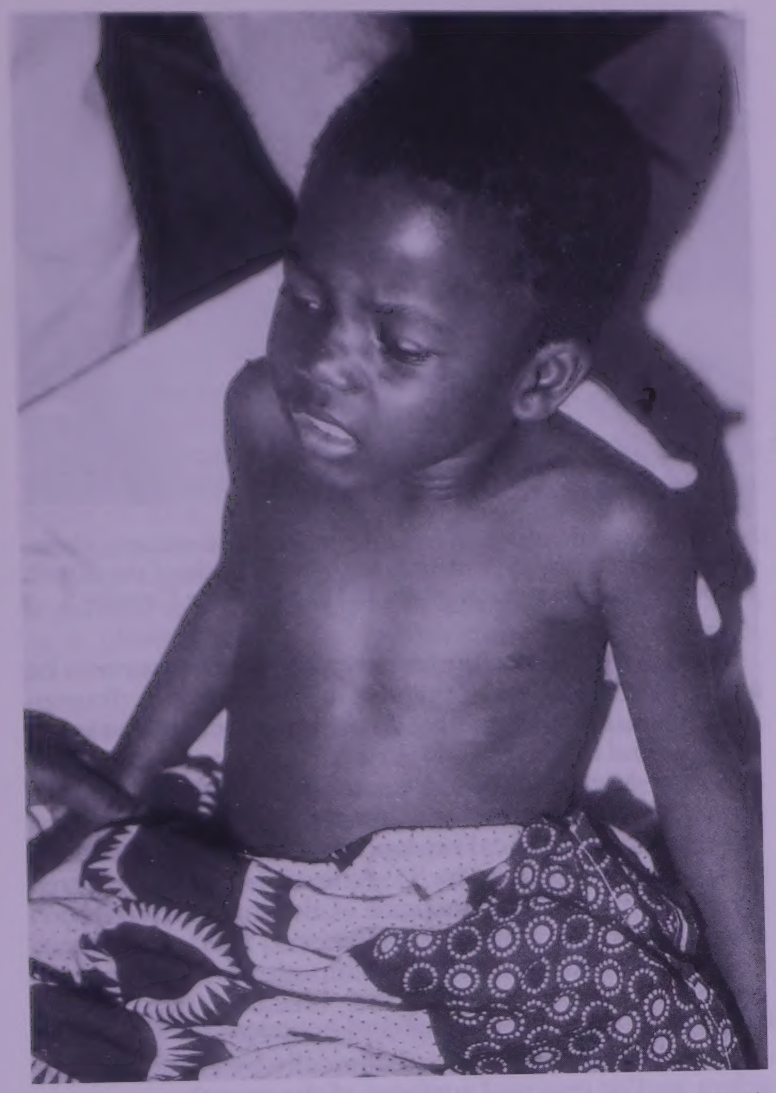

Fig. 1. Testing for 'prostration': inability to sit up unsupported. (©D. A. Warrell.)

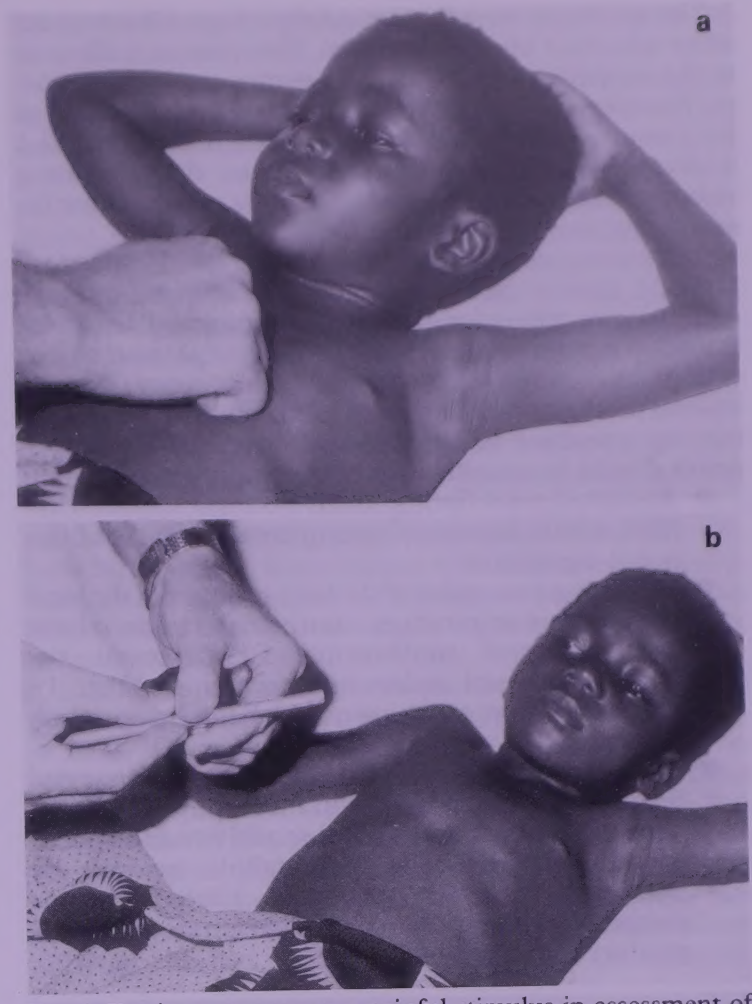

Fig. 2. Testing response to a painful stimulus in assessment of the Glasgow or Blantyre coma scores by (a) rubbing knuckles on the patient's sternum or (b) pressing a pencil on the nail bed. (©D. A. Warrell.)

Fig. 3. Determining eye movement in assessment of the Blantyre coma score: following the mother's face (©D. A. Warrell.)

based on history. Many children who are pyrexial and feel unwell prefer to lie or be carried but are capable of sitting if gently encouraged to do so (Fig. 1). In adults prostration is usually manifested as extreme weakness.

Impaired consciousness. This should be assessed using the Blantyre coma scale for children (Table 3) (MOLYNEUX *et al.*, 1989a) and the Glasgow Coma scale for adults (Table 5; see p. S1/11) (TEASDALE & JENNETT, 1974). Other coma scores may also be useful and improved methods of assessing very young children have been proposed (NEWTON *et al.*, 1997a). However, whatever methods are used, the Blantyre coma score should also be recorded to allow comparability between series and comparison of children with the same depth of coma. The use of the Blantyre score requires careful local standardization. Care must be exercized in applying the stimuli; it is unkind and unnecessary to test responses repeatedly. Testing should begin with a minimal stimulus which should be increased only to the point where a clear response is obtained (Fig. 2a, b). A localizing response must be distinguished from a brisk flexion response which brings the hand into coincidental proximity to the stimulus. The interpretation of 'verbal cry' is difficult, some children are stoical and the appropriateness of verbal response needs to be considered in the light of other responses and the age of the child. It is best to test orientation by asking the mother to move her face across the child's field of vision (Fig. 3) as the child may be less interested in looking at a stranger's face.

The term 'cerebral malaria' has been reserved for patients unable to localize a painful stimulus (WARRELL *et al.*, 1982). In some series this has been approximated by a Blantyre coma score of 2 or less. This is usually true, but some children may score 3 on the coma scale despite failing to localize a painful stimulus. This is especially the case in children aged between 9 and 15 months who have only recently acquired the ability to localize a painful stimulus (8–9 months).

Factors affecting assessment of impaired consciousness. Many children with malaria recover full consciousness after a convulsion and it is important to exclude transient post-ictal coma. Unfortunately, this is not clear-cut as the post-ictal phase may be longer than that observed with the usual febrile fits of childhood (CRAWLEY *et al.*, 1996). Previous recommendations have suggested delaying assessment until 6 h (WARRELL *et al.*, 1982) or at least 30 min (WARRELL *et al.*, 1990) after a seizure. Experience has indicated that a substantial group of children does not regain full consciousness until between 30 min and 1 h. Assessment for clinical management purposes should therefore be made immediately, but for classification for research studies the assessment should be repeated at 1 h.

The use of anticonvulsant or sedative drugs. Children are often admitted after being given diazepam at a clinic or in the outpatient department; this may impair responses. For consistency the approach should be the same as for a convulsion: i.e., assessment should be repeated 1 h after administration of diazepam and the fact that a sedative drug has been given should be recorded for research purposes as well as in the clinical notes.

Respiratory distress (acidotic breathing). Respiratory rate and pattern can be assessed only in a child who is not crying or otherwise disturbed. Respiratory distress is a useful summary description for clinical assessment which has good interobserver consistency among trained medical workers (ENGLISH *et al.*, 1996a, 1996d) but the presence of the following individual components should be specified for research purposes.

- *Sustained* nasal flaring; many younger children exhibit minor degrees of intermittent flaring, but this is not significant.
- *Indrawing (recession) of the bony structure of the lower chest wall* on inspiration; many small children have visible inward movement of intercostal tissues—intercostal indrawing (recession) (Fig. 4); this should not on its own be labelled respiratory distress.
- *Deep breathing* (acidotic breathing, Kussmaul breathing) is the most important respiratory sign of severe malaria as it has good sensitivity and specificity for the detection of metabolic acidosis by trained observers (ENGLISH *et al.*, 1996a). The important component is increased inspiratory and expiratory excursion of the chest.

Fig. 4. Retraction (recession of the intercostal spaces) in a child with respiratory distress associated with metabolic acidosis in severe malaria. (©D. A. Warrell.)

Multiple convulsions. Many children with malaria have convulsions. In the absence of severe malaria, generalized seizures were associated with a 9-fold increase in risk of a fatal outcome in children (WATTANAGOON *et al.*, 1994). The length, nature and number of convulsions should be recorded. Many convulsions associated with malaria are focal and care should be taken to detect minor manifestations such as twitching of a digit, repetitive jerky eye movements with deviation (Fig. 5), increased salivation or abnormal respiratory patterns.

Circulatory collapse. It is difficult to provide exact definitions for small children, not least because children who become shocked with malaria often deteriorate very rapidly. Core-to-skin temperature differentials have not proved sensitive or specific in African children with malaria (M. English, personal communication). The diagnosis must be based on a combination of hypotension and poor perfusion (cool peripheries, especially mid to proximal limb coolness, and weak or absent peripheral pulses). It should be noted that accurate blood pressure measurement in young children depends on using the correct cuff size.

Fig. 5. Focal convulsion in a child with cerebral malaria, showing deviation of the eyes, twitching of the left side of the mouth and stereotyped elevation of the left arm. (©Jane Crawley.)

Pulmonary oedema. Pulmonary oedema appears to be a rare manifestation of malaria in children, but diagnosis is often difficult and really requires a chest X-ray*.

Abnormal bleeding. This is rare in children with severe malaria. A check should be made for bleeding from gums, nose, gastrointestinal tract or venepuncture sites. When possible clinical evidence of bleeding should lead to appropriate laboratory investigations (platelets, prothrombin time and a measure of the intrinsic pathway, e.g., kaolin cephalin time). However, mild abnormalities of laboratory indices are common and, in the absence of clinical evidence of bleeding, are not in themselves an indication of severe disease.

Jaundice. This is detected clinically by examining the sclera and/or mucosal surfaces of the mouth.

Haemoglobinuria. When the urine is dark red or black, and the urinanalysis dipstick test is positive for haemoglobin/myoglobin, the absence of microscopic haematuria suggests either haemoglobinuria or myoglobinuria.

Severe anaemia. Haemoglobin should be measured using a haemoglobinometer or automated counter. As an alternative, packed cell volume may be measured. Severe anaemia is defined as haemoglobin <5 g/dL or haematocrit <15%. It should be specified whether results are from a finger prick or venous sample. Finger prick samples may underestimate the haemoglobin concentration by a gram or more if the finger is squeezed during collection. If facilities are available, the mean corpuscular volume (MCV) should be recorded but microcytosis does not exclude the diagnosis of severe malarial anaemia as malaria and iron deficiency commonly co-exist and interact.

Hypoglycaemia. This is defined as a whole blood glucose concentration of less than 2.2 mmol/L (less than 40 mg/dL). For screening purposes, methods using dip sticks and a reflectometer are useful. However, they are less accurate below 3 mmol/L and tend to overestimate the prevalence of hypoglycaemia. For research purposes hypoglycaemia should be confirmed on a venous sample measured with a glucose analyser.

Acidosis. This should be specified as a plasma bicarbonate concentration (<15 mmol/L) or base excess (>–10). The acidaemia which may accompany acidosis is defined as pH <7·35 measured in capillary or arterial blood.

If the patient's core temperature is higher than the temperature at which arterial blood pH is measured (electrode temperature is usually maintained at 37°C),

*The radiological features of progressive pulmonary oedema in children are: increased interstitial markings; hazy peri-hilar interstitial shadowing; frank air-space disease with focal or conglomerate shadowing and air bronchograms; and 'bat's-wing' shadowing and Kerly B lines with or without pleural effusion.

a correction must be applied. 0·0147 pH units must be added to the measured pH for each degree Celsius (°C) the patient's temperature is higher than the temperature of the pH electrode (ROSENTHAL, 1948; ADAMSON *et al.*, 1964).

Hyperlactataemia. The normal range for plasma lactate is up to 2 mmol/L. A level >5 mmol/L is an indication of severe malaria (KRISHNA *et al.*, 1994a).

Hyperparasitaemia. The relation of parasitaemia to severity of illness is different in different populations and age groups. In non-immune children in areas of unstable endemicity, a peripheral parasitaemia of 4% or more carries an increased risk of death and should be considered a sign of severe malaria (LUXEMBURGER *et al.*, 1994). In areas of stable endemicity, threshold levels should be derived from local experience but, in the absence of data, a parasitaemia ≥20% should be considered to indicate severe malaria.

Renal impairment. Renal failure is rare in children. It is defined as a urine output of less than 12 mL/kg/24 h or a plasma creatinine concentration above the age-related normal range, persisting after rehydration.

Clinical features of severe falciparum malaria in children

Most of the estimated over one million malaria deaths every year are in children up to 5 years old who live in areas of intense transmission of *P. falciparum*, especially in sub-saharan Africa (WHO, 1996).

Many studies in such areas describe a pattern of severe disease that differs considerably from that seen in non-immune adults (see Table 4). It is uncertain whether these differences in the clinical manifestations of severe disease are due mainly to the age of affected individuals, or to other differences between populations in the characteristics of host, parasite, pattern of exposure, or provision of health services.

There are fewer data on the pattern of clinical disease in children outside Africa. In Viet Nam the incidence of renal failure as a complication of falciparum malaria is intermediate between that in non-immune adults and the very low incidence in African children (D. Bethell and N. M. Dung, personal communication).

Within sub-saharan Africa there are areas with low or epidemic transmission, where severe malaria occurs more commonly in adults than it does elsewhere in Africa (ENDESHAW *et al.*, 1991).

The influence of transmission intensity and seasonality on the disease pattern in children is not known, because there have been few studies of the spectrum of malaria disease and mortality in areas of different endemicity. Existing data suggest that in populations subjected to very high inoculation rates throughout the year, severe anaemia may be the commonest complication, affecting mainly infants and very young children, while in areas with less intense or seasonal transmission, cerebral malaria in slightly older children may predominate (SLUTSKER *et al.*, 1994; SNOW *et al.*, 1994; SNOW & MARSH, 1998).

Malaria in infancy. Babies born to mothers who have malaria during pregnancy are at risk of having a lower birth weight than the community average, usually as a result of intrauterine growth retardation (see p. S1/19). Low birth weight is associated with increased mortality from all causes in infancy, although a specific contribution of malarial low birth weight to this mortality has not been shown (STEKETEE & WIRIMA, 1996).

In endemic areas neonates may have cord blood and peripheral parasitaemia, which disappears within hours or days. 'Congenital' malaria (illness in the neonate resulting from malarial infection) is rare, but may present as neonatal jaundice (see p. S1/19–S1/20). Over the first few months of life, parasitaemia appears in an increasing proportion of children, the rate of increase in prevalence being a measure of transmission intensity. The great majority of infections are probably symptomless, although this fact is difficult to establish in a community in which there are frequent childhood ailments from a variety of possible causes. The likelihood of symptoms increases with the density of parasitaemia, allowing statistical calculations of malaria-attributable morbidity (SMITH, T. *et al.*, 1994).

From the age of a few months onwards, infected infants may develop severe disease. Some studies have suggested that about one infection in a hundred progresses to cause complications (GREENWOOD *et al.*, 1991). These figures and the case fatality rates of severe disease probably differ between populations according to the transmission characteristics, health service provisions, parasite drug sensitivities and a variety of parasite

Table 4. Diffferences between severe malaria in adults and children

	Adults	Children
Cough	Uncommon early symptom	Common early symptom
Convulsions	Indicate cerebral involvement or hypoglycaemia	May indicate cerebral involvement or hypoglycaemia, but may be non-specific consequence of fever
Duration of symptoms before features of severe disease develop	Commonly several days	Usually 1–2 d only
Jaundice	Common	Uncommon
Time from start of treatment to resolution of coma in cerebral malaria	Usually 2–4 d	Usually 1–2 d
Hypoglycaemia	Relatively uncommon. Usually quinine-induced (especially in pregnancy) with hyperinsulinaemia. Sometimes pre-treatment with low plasma insulin	Common. Usually pre-treatment, with decreased circulating insulin
Pulmonary oedema	Common	Rare
Susceptibility to toxicity of antimalarial drugs	See above *re* quinine-induced hypoglycaemia in adults	More liable than adults to suffer circulatory collapse after parenteral chloroquine (but schedules in Tables 9 & 10 are safe)
Renal failure	Common	Rare
Neurological sequelae after cerebral malaria	Uncommon	Occur in about 10% of cases

and host factors. The mortality rates for acute falciparum malaria with access to antimalarial treatment on the eastern border of Thailand in 1986 and on the western border of Thailand in 1991–1992 were similar, approximately 1:1000 cases of acute falciparum malaria (MEEK *et al.*, 1986; LUXEMBURGER *et al.*, 1996).

Importance of malaria as a cause of mortality in children. Malaria is one of the 3 commonest reasons for admission to hospital, and is one of the commonest causes of hospital death in children aged 1–5 years, in many endemic areas (GREENWOOD *et al.*, 1987). Large-scale intervention studies with impregnated bed nets suggested that malaria contributes to as much as half of all mortality in children aged between 1 month and 5 years (ALONSO *et al.*, 1993; NEVILL *et al.*, 1996).

It is likely that most children who die of malaria do so without reaching any kind of health facility (GREENWOOD *et al.*, 1987; SNOW *et al.*, 1994). The relative contributions of various syndromes to mortality among those not receiving health care is difficult to assess, because of the unreliability of 'verbal autopsy' as a method of retrospective diagnosis, especially for malaria and its complications (SNOW *et al.*, 1992).

Relative importance of different syndromes in fatal malaria. Traditionally, severe malaria in African children has been considered to fall into two main categories—severe anaemia and cerebral malaria. Recent evidence indicates that metabolic acidosis, presenting as the clinical syndrome of respiratory distress (particularly deep breathing), is an important feature of severe malaria that may present separately or in combination with one or both of the traditionally recognized categories (MARSH *et al.*, 1995).

The presence of impaired consciousness or severe respiratory distress predicted 84% of 64 deaths among 1844 children admitted with malaria to a district hospital in coastal Kenya. In this study severe anaemia was common but rarely fatal unless accompanied by impaired consciousness or severe respiratory distress. Hypoglycaemia and jaundice were both associated with an increased case fatality rate, but were associated with only 31% and 16% of deaths respectively, all of these deaths being among children with coma or respiratory distress.

The pattern of clinical events associated with death may be different in the absence of hospital treatment.

In Nigeria, 46·5% of 147 children with fatal *P. falciparum* infections had cerebral malaria (ELESHA *et al.*, 1993). In The Gambia, 43% of children admitted to hospital over a period of several years, and diagnosed as having severe malaria, were in coma (WALLER *et al.*, 1995); the proportion was similar — 50% — in a series in Burkina Faso (MODIANO *et al.*, 1995), but considerably less in a series in Madang, Papua New Guinea where, of 249 children admitted to hospital with severe malaria, 56 (22%) were comatose; in the same series 155 (62%) of the children admitted had severe anaemia (ALLEN *et al.*, 1997).

The problem of distinguishing between severe malaria and pneumonia. Several studies have demonstrated the difficulty of distinguishing clinically between pneumonia and malaria. In Malawi, of 471 children attending a hospital outpatient department who fulfilled the WHO clinical definition for pneumonia, 449 (95%) also met the clinical definition of malaria (REDD *et al.*, 1992). Among Gambian children with cough or breathing difficulty and a raised respiratory rate, 38% had only malaria (parasitaemia with normal chest radiograph) in the season of intense malaria transmission, compared to 6% during the season of low malaria transmission (O'DEMPSEY *et al.*, 1993). In Kenya, ENGLISH *et al.* (1996e) studied 200 children with fever, cough tachypnoea and additional features of respiratory distress, and selected for comparison 26 children with definite pneumonia (radiological consolidation, no parasitaemia) and 38 children with definite malaria (normal chest radiograph, parasitaemia >100 000 μL); chest indrawing, unilateral signs and crackles or wheeze were significantly associated with pneumonia, and pallor and deep breathing with malaria, but no group of signs was entirely specific or sensitive for either diagnosis.

These observations indicate the need to consider and treat for both malaria and pneumonia in children with fever and chest symptoms in malarious areas, especially where either radiological or microscopical facilities are not available (BLOLAND *et al.*, 1991).

Cerebral malaria

Impaired consciousness. A number of different disease processes may affect consciousness in the child with malaria, including convulsions, hypoglycaemia, hyperpyrexia, acidosis, severe anaemia and sedative drugs. However, coma may develop in the absence of any of these causes (see section on pathogenesis, pp. S1/24–S1/25).

In most published studies the term 'cerebral malaria' has been restricted to the syndrome in which altered consciousness, associated with a malaria infection, could not be attributed to convulsions, sedative drugs or hypoglycaemia alone or to a non-malarial cause. A child with loss of consciousness after a febrile convulsion should not be considered to have cerebral malaria unless coma persists for more than one hour after the convulsion. Similarly, in a child with malaria and hypoglycaemia who is comatose, diagnosis of cerebral malaria cannot be sustained if consciousness is promptly restored by administration of glucose. 'Cerebral malaria' is a clinical syndrome; this term is convenient for descriptive purposes.

Preceding symptoms. In children with cerebral malaria who are admitted to hospital, the duration of febrile symptoms is usually short. In a series of 131 patients studied in Malawi, the mean length of reported history was 47 h (range 2 h to 7 d) (MOLYNEUX *et al.*, 1989b); in 195 Zambian children with cerebral malaria, the median duration of preceding fever had been 49·3 h (range 0 to 13 d) (MABEZA *et al.*, 1995). The earliest symptom is usually fever, which is followed by failure to eat or drink. Vomiting and coughing were reported in the majority of cases in Malawi; diarrhoea is an unusual symptom. Convulsions are common before or after the onset of coma (see below).

General features. Most but not all children with cerebral malaria are febrile. Rectal temperatures range from 36°C to 41°C or even higher. Dehydration is present in many cases (WALLER *et al.*, 1995; ENGLISH *et al.*, 1996c), but is rarely severe. The systolic blood pressure is usually normal but there is a wide pulse pressure. Most patients have a tachycardia appropriate to their fever. Cardiac arrhythmias are rare. Breathing may be rapid, or laboured; deep breathing suggests acidosis (see below). Examination of the heart and lungs is usually normal. A minority of patients have cold, clammy skin with a core-to-skin temperature difference greater than 10°C. Some of these patients are in a state of shock with systolic blood pressure below 50 mmHg. Jaundice is reported to be less common in children than in adults with cerebral malaria (WHITE *et al.*, 1987a; MOLYNEUX *et al.*, 1989b). Hepatosplenomegaly is commonly found at the time of presentation or during the course of the disease. Retinal haemorrhages are seen in some patients (KAYEMBE *et al.*, 1980; LEWALLEN *et al.*, 1993, 1996), but spontaneous bleeding into the skin or gastrointestinal tract is rare.

Neurological features. The depth of coma may be assessed by observing the response to standard painful or vocal stimuli (see Table 3 and Figs 2a, b & 3). The gag reflex is usually but not invariably preserved. In patients with profound coma, corneal reflexes and oculocephalic 'doll's-eye' reflexes may be abnormal, and there may be abnormalities of conjugate gaze. Corneal and pupillary light reflexes are usually retained. Retinal abnormalities

Fig. 6. Multiple retinal haemorrhages in a child with cerebral malaria. (©K. Marsh.)

are found relatively commonly in cerebral malaria, particularly if indirect ophthalmoscopy is used as well as conventional direct ophthalmoscopy. Five distinct clinical entities have been reported: (i) retinal haemorrhages (Fig. 6), (ii) 'cotton wool' spots, (iii) papilloedema, (iv) retinal whitening (in earlier reports referred to as 'oedema') and (v) retinal vessel abnormalities. Retinal haemorrhages were found in 37% of children with cerebral malaria in the Malawi series, in 16% of Zambian children with cerebral malaria (HASLETT, 1991), in 15% of children with severe malaria in Papua New Guinea (ALLEN *et al.*, 1997), and in 6–8% of African children in other series (NEWTON *et al.*, 1991; WALLER *et al.*, 1995; HERO *et al.*, 1997). Haemorrhages are usually round and intra-retinal in location, although preretinal haemorrhages may also be seen. Approximately half the haemorrhages have a pale centre. 'Cotton wool' spots occur in approximately 5% of African children and papilloedema in 8%. The incidence in adults is lower. Discrete spots of retinal whitening or opacification which are deep to the retinal vessels have been described in approximately 30% of Malawian children (LEWALLEN *et al.*, 1996, 1998, 1999). Although associated with severe disease, retinal haemorrhages do not appear to have prognostic significance for mortality.

In both adults and children with severe malaria colour changes from either pink (arterial) or blue (venous) to orange or white may be seen in a localized segment of retinal vessel (LEWALLEN *et al.*, 1998).

Abnormalities of muscle tone and posture are frequently seen (REY *et al.*, 1966; DUMAS *et al.*, 1986; MOLYNEUX *et al.*, 1989b; MABEZA *et al.*, 1995; WALLER *et al.*, 1995). These may take the form of muscular hypotonia (Fig. 7) or, more commonly, of decerebrate or decorticate posturings, which may be intermittent or sustained. In some children extreme opisthotonos is seen (Fig. 8), which may misleadingly suggest a diagnosis of tetanus or meningitis. Bruxism (grinding of teeth) is common (Fig. 9). Plantar reflexes are sometimes abnormal, and abdominal reflexes are almost invariably absent.

Fig. 7. Flaccid tone (hypotonia; 'broken neck syndrome') in a child recovering from cerebral malaria. (©D. A. Warrell.)

Fig. 8. Opisthotonos in an unrousably comatose child with cerebral malaria; the cerebrospinal fluid cell count was normal. (©M. E. Molyneux.)

Fig. 9. Grinding of the teeth ('bruxism') in a girl with cerebral malaria. (©D. A. Warrell.)

Convulsions. Over 50% of children with cerebral malaria have convulsions. Cerebral malaria was considered

to be the cause of convulsions in one-third of children admitted to a Nigerian hospital in 1988 (ASINDI *et al.*, 1993). Convulsions may be generalized or focal, single or recurrent and, unlike febrile convulsions, may occur in children of any age (REY *et al.*, 1966) and at any level of body temperature (MOLYNEUX *et al.*, 1989b). In some patients (about 25% of children with cerebral malaria in a Kenyan hospital), seizure activity can be demonstrated by electroencephalography in the presence of only minor, if any, convulsive movements of limbs or facial muscles but with jerky eye movements with deviation (Fig. 5), excessive salivation and irregular breathing patterns (non-convulsive status epilepticus) (CRAWLEY *et al.*, 1996).

Intracranial pressure. This is increased in the majority of children with cerebral malaria (NEWTON *et al.*, 1991). The mechanism and pathophysiological importance of raised intracranial pressure is uncertain. Raised intracranial pressure, while not responsible for coma or for most of the presenting neurological features, may contribute to death in some patients with cerebral malaria. This topic is discussed more fully in the section on pathophysiology (pp. S1/25–S1/26).

Hypoglycaemia. Hypoglycaemia (see below) is frequently found in children with cerebral malaria (WHITE *et al.*, 1987a; TAYLOR *et al.*, 1988). It is associated with appropriately low plasma insulin concentrations and is commonly accompanied by hyperlactataemia. The low plasma insulin level represents an appropriate response to hypoglycaemia and indicates that hypoglycaemia is not due to hyperinsulinaemia.

Acidaemia. Acidaemia was present on admission in 42% of 141 children with cerebral malaria in Malawi (TAYLOR *et al.*, 1993), and 62 of 332 (19%) children with impaired consciousness due to malaria in Kenya (MARSH *et al.*, 1995). Capillary blood pO_2 and arterial blood oxygen saturation are normal in nearly all patients with cerebral malaria. Plasma urea and creatinine concentrations may be elevated on admission, especially in the presence of moderate dehydration; values revert to normal during treatment (ENGLISH *et al.*, 1996b). Acute renal failure is rare. In adults, hyponatraemia has been attributed to inappropriate secretion of antidiuretic hormone (MILLER, L. H. *et al.*, 1967; HOLST *et al.*, 1994). Hyponatraemia was found in 55% of 132 children with severe malaria in Kenya. It was rarely attributable to inappropriate secretion of antidiuretic hormone (ENGLISH *et al.*, 1996c). Chest radiographs are usually normal, even in the presence of deep or laboured breathing; this is further evidence that pulmonary oedema or 'adult respiratory distress syndrome' (ARDS) is rare in children.

Recovery from cerebral malaria. The reported hospital case-fatality rate of cerebral malaria in children has ranged from 10% to 40%, but in recent studies the average case-fatality rate was about 16% (DUMAS *et al.*, 1986; WHITE *et al.*, 1987a; MOLYNEUX *et al.*, 1989b; WALLER *et al.*, 1995). Most deaths in children admitted to hospital occur within the first 24 h of treatment. In survivors, the duration of altered consciousness after the start of treatment ranges from a few hours to several days, the mean being about 30 h in Malawi and the median 12 h in The Gambia (WHITE *et al.*, 1987a). The transition from coma to full consciousness is sometimes very rapid, and may not be witnessed unless frequent observations are made. In some children, recovery of consciousness may represent the end of a post-ictal state, or emergence from a drug-induced stupor; these conditions cannot be distinguished from cerebral malaria, but the timing of recovery may be suggestive.

Neurological sequelae after cerebral malaria in children. The majority of children who survive cerebral malaria make a full neurological recovery, but some are left with neurological sequelae. Among 11 African series including a total of 1341 cases of cerebral malaria, the rate of neurological sequelae was 6·7% and the case-fatality rate was 19% (COMMEY *et al.*, 1980; OMANGA *et al.*, 1983; SCHMUTZHARD & GERSTENBRAND, 1984; BOJANG *et al.*, 1997). Methodological differences between the studies limit the comparisons that can be made, but 4 more recent studies from Malawi (MOLYNEUX *et al.*, 1989b), The Gambia (BREWSTER *et al.*, 1990), Nigeria (BONDI, 1992), and Kenya (N. M. Peshu, personal communication) have used essentially similar criteria: in these studies a total of 1060 children was reported, with an overall incidence of neurological sequelae of 11·5% (13·3% in survivors) and a case-fatality rate of 13·5%. The most common sequelae in these studies were ataxia (43%), hemiplegia (39%), speech disorders (39%) and blindness (30%). Other sequelae reported at discharge included behavioural disturbances, hypotonia, generalized spasticity and a variety of tremors. SOWUNMI *et al.* (1993) described 2 children with visual and auditory hallucinations a few days after recovery from cerebral malaria.

Most patients with sequelae show considerable improvement with time (SCHMUTZHARD & GERSTENBRAND, 1984; BONDI, 1992), but neurological symptoms may persist. The most complete study was carried out in Kenya where 63 children with cerebral malaria had sequelae on discharge from hospital; 90% were successfully followed up for at least a year or until they died. Eight (14%) of the children died as a direct result of severe sequelae (N. M. Peshu, personal communication). Major persisting neurological sequelae in the 4 recent studies in Africa were hemiplegia (42%), speech disorders (28%), behavioural disorders (24%) and epilepsy (24%). Less frequent permanent sequelae included blindness (8%) and cerebral palsy (6%). Cortical blindness showed the most dramatic resolution. In different series, between 80 and 90% of children with cortical blindness recovered their sight fully. However, in a recent study from The Gambia, sequelae were rare (MUNTENDAM *et al.*, 1996). Findings in Papua New Guinea differed from those in Africa: among 62 children surviving cerebral malaria, several had unsteadiness of gait on discharge from hospital, but none had persisting neurological sequelae after one year of follow-up (S. J. Allen, personal communication). The risk of minor cognitive dysfunction is uncertain, but 2 large prospective studies are now in progress. Preliminary results from studies of 87 matched pairs of cases and controls on the coast of Kenya suggest that ability to perform memory tasks, information processing and intelligence quotient (IQ) are unimpaired but that there may be some defect of cognitive function (P. Holding, personal communication).

Prognostic factors associated with sequelae are similar, but not identical, to those predicting mortality (see below). Computed tomography of the brain in 14 Kenyan children recovering from cerebral malaria revealed evidence of brain swelling in 6 and of ischaemic damage in 4, all of whom suffered from neurological sequelae (NEWTON *et al.*, 1994) (Fig. 10).

Hypoglycaemia

Children are more likely than adults to develop hypoglycaemia, and may become hypoglycaemic solely as a result of fasting, particularly during any illness accompanied by fever and vomiting. Hypoglycaemia was found in 43 of 603 children (7%) admitted to hospital in Mozambique, in association with a variety of clinical conditions including malnutrition, pneumonia and malaria (SOLOMON *et al.*, 1994).

Hypoglycaemia (whole blood glucose <2·2 mmol/L) commonly complicates severe malaria in children, and is associated with an increased risk of dying or suffering sequelae from the illness (WHITE *et al.*, 1987a; TAYLOR *et al.*, 1988). Hypoglycaemia is particularly common in young children (<3 years old), in those with convulsions or hyperparasitaemia, and in patients with profound coma. It is associated with convulsions, lactic acidosis and

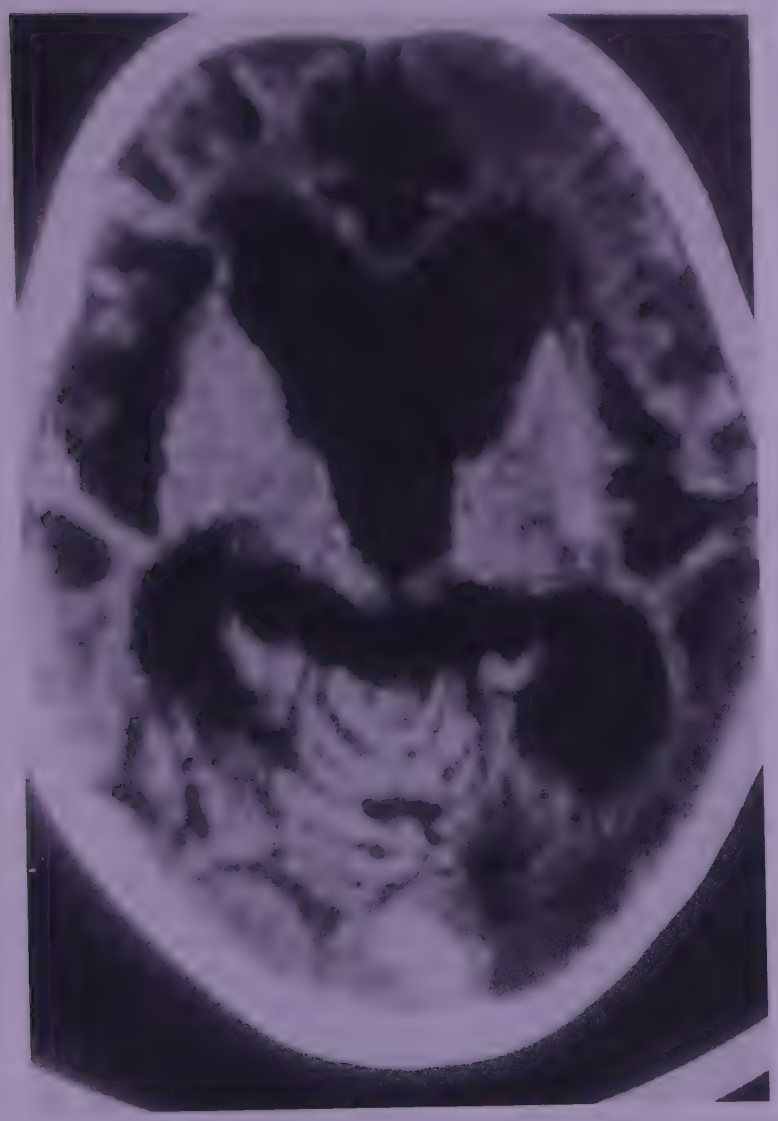

Fig. 10. Computerized tomography scan of the brain of a child who had recovered from cerebral malaria, but had severe neurological sequelae; there is evidence of extensive ischaemic damage. (©C. R. J. C. Newton.)

high concentrations of circulating tumour necrosis factor. Hypoglycaemia is easily overlooked clinically because the manifestations may be similar to those of cerebral malaria. In a child with impaired consciousness, correction of hypoglycaemia with intravenous 50% dextrose may not result in immediate restoration of consciousness.

Hypoglycaemia may recur during treatment of severe malaria; these recurrences are commonly due to the disease (plasma insulin concentrations are appropriately low) but quinine-induced hyperinsulinaemia may contribute to recurrent hypoglycaemia in some cases.

Recurrent hypoglycaemia may be impossible to suspect clinically in the comatose child, or may cause deepening coma or convulsions.

Acidosis

In a variety of severe disease states, including severe malaria, the presence of acidaemia is associated with a high mortality rate (STACPOOLE *et al.*, 1994).

Acidaemia is a manifestation of severe malaria, whether there is altered consciousness or not (TAYLOR *et al.*, 1993; KRISHNA *et al.*, 1994a; MARSH *et al.*, 1995; WALLER *et al.*, 1995). In a selected group of Malawian children admitted to hospital with a primary diagnosis of malaria, 66 of 145 (46%) were found to be either acidaemic, with a pH less than 7·3, or having compensated metabolic acidosis (TAYLOR *et al.*, 1993); 72% of children who subsequently died were acidotic on admission. 42% of children with cerebral malaria were acidaemic and mortality in these children was 28% compared to 3% in the non-acidaemic group (relative risk of death for acidaemic group=8·5). Acidosis was the major independent risk factor for death but was also strongly associated with hypoglycaemia, a known risk factor for death in malaria; all 14 hypoglycaemic patients were acidotic. Lactic acidosis appears to be the major (but not the only) contributing mechanism of acidosis. Serial clinical and metabolic changes were reported in 115 Gambian children with severe malaria (KRISHNA *et al.*, 1994a), of whom 21 died. After treatment, lactate concentration fell rapidly in survivors but fell only slightly, or rose, in fatal cases. It is in the minority of patients whose hyperlactataemia does not resolve in the first few hours of admission that the prognosis is worse.

In Kenya severe metabolic acidosis (base excess ⩾−12) was strongly associated with risk of death (relative risk=8) in a series of 299 children with severe malaria. In a series of 115 children with severe malaria in The Gambia, pH was not measured but mean venous blood lactate was almost twice as high in fatal cases.

Among 1844 children admitted consecutively to Kilifi hospital on the Kenyan coast with a primary diagnosis of malaria, 14% had respiratory distress (nasal flaring, indrawing [recession] of the bony structure of the chest wall, or deep breathing), of whom 14% died. 55% of all children with malaria who subsequently died had respiratory distress on admission. Over 80% of a subgroup of these children with respiratory distress proved to be profoundly acidotic (MARSH *et al.*, 1995).

The relative importance of the clinical syndrome of respiratory distress and its overlap with impaired consciousness and severe anaemia are shown in Fig. 11 (MARSH *et al.*, 1996). As has been reported in western Kenya, respiratory distress was an important prognostic factor for the death in children with severe anaemia in Kilifi but it was an equally important prognostic index in those not severely anaemic. The highest mortality occurred in children with both neurological impairment and respiratory distress.

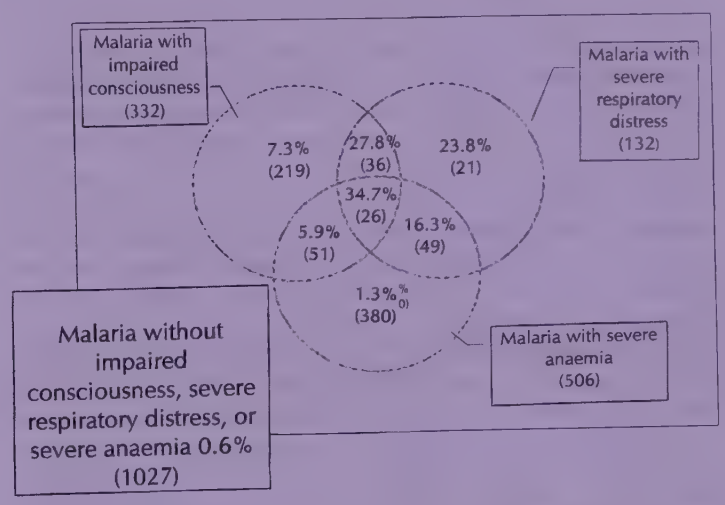

Fig. 11. Relative importance of the clinical syndrome of respiratory distress (acidosis) and its overlap with impaired consciousness and anaemia in a group of 1844 African children (MARSH *et al.*, 1995). Total numbers are given in parentheses and mortality rates as percentages of these totals. (Some children had more than one condition, so the percentages add up to more than 100.)

It is likely that different factors may contribute to lactic acidosis in different individuals. Underlying mechanisms include impaired hepatic function and sequestration in the microvcasculature. However, from a practical point of view, hypovolaemia, anaemia and renal impairment seem to be particularly important (ENGLISH *et al.*, 1997).

Deep breathing is an accurate clinical indicator of the presence of acidosis (ENGLISH *et al.*, 1996a). Acidosis is associated with recent convulsions and with hypoglycaemia and anaemia. Lactic acidosis is a major contributor to acidaemia, and probably results more from tissue anoxia and anaerobic glycolysis than from the release of lactate by parasitized erythrocytes (KRISHNA *et al.*, 1994a).

Fig. 12. Profound anaemia (haemoglobin concentration 1·2 mg/dL) in an African child, resulting from repeated attacks of malaria. (©D. A. Warrell.)

Anaemia

Anaemia is an important and commonly life-threatening complication of falciparum malaria in children (Fig. 12). The mean age of children presenting with severe malaria anaemia is about 1·8 years, compared to 3 years in those presenting with cerebral malaria.

Of 2433 children admitted to a Kenyan hospital in 1990, 684 (29%) had severe anaemia (haemoglobin <5·0 g/dL), this being strongly associated with *P. falciparum* parasitaemia; 18% of the severely anaemic patients died, compared to 8% of all admissions (LACKRITZ *et al.*, 1992). In this and in another study in Kenya (MARSH *et al.*, 1995), the mortality among anaemic children was greatly increased when there was associated respiratory distress. Blood transfusion reduced the case fatality rate in children with anaemia and respiratory distress (LACKRITZ *et al.*, 1992). In this study, blood transfusion given after a delay of 2 d was not beneficial, suggesting that mortality due to severe anaemia may be considerably greater in the community than in hospital where prompt treatment can be given. Community deaths from severe anaemia are difficult to identify in retrospect because of the poor sensitivity and specificity of verbal autopsies for the diagnosis of anaemia (SNOW *et al.*, 1992).

Among 252 Malawian infants followed for the first year of life, 25% had a haematocrit below 25% by 2 months of age; anaemia at this age was statistically associated with placental parasitaemia at birth (REDD *et al.*, 1994).

It is commonly said that breathing difficulty in a severely anaemic child is due to 'congestive cardiac failure'; this supposition has been questioned (ENGLISH *et al.*, 1997), in the light of evidence that in many severely anaemic children the cause of respiratory distress is acidosis, resulting from impaired oxygen supply to poorly perfused tissues.

Anaemia may develop rapidly during the course of malarial illness, especially if there is initial hyperparasitaemia (MCGREGOR *et al.*, 1956). Anaemia may be present or may develop in a child with cerebral malaria or any other complication of *P. falciparum* infection. Severe anaemia may, however, be the only or predominant complication of malaria in a child presenting to a health facility; in this circumstance, and in a child found to have severe anaemia in a community survey, the rapidity of onset of anaemia cannot be determined. Severe anaemia is often multifactorial, and is attributable to malaria because of parasitaemia and the lack of an adequate alternative explanation.

Respiratory distress

Respiratory distress is a summary description applied to children who have obviously abnormal breathing involving the expenditure of more effort than usual. There are 2 major components which may both contribute to this impression. Deep breathing involves an abnormally increased amplitude of chest excursion. It is a sign of metabolic acidosis. The increased depth of respiration may be accompanied by a degree of intercostal indrawing (recession) (Fig. 4), particularly in thin children with notably raised respiratory rate, but this is in proportion to the overall increase in effort and is not prominent. The second possible component is true indrawing of the bony structures of the lower chest wall. This can be a sign of lung disease, usually pneumonia, or of metabolic acidosis, and is usually associated with increased use of accessory muscles. In practice, most cases of respiratory distress in association with malaria involve deep breathing secondary to metabolic acidosis. However, in a small proportion of cases there is concomitant pneumonia, so the presence of either component of respiratory distress should be regarded as a danger sign. Although the respiratory rate will usually be raised above the age-related normal value, the actual degree of tachypnoea does not correlate well with the overall impression of distress, whether it be due to metabolic acidosis or parenchymal disease. In fact, progressively severe metabolic acidosis may be associated with a decrease in respiratory rate, as the pattern of respiration changes from 'panting' to 'air hunger' (Kussmaul's respiration).

Respiratory distress is a major risk factor for death in children with malaria (LACKRITZ *et al.*, 1993; MARSH *et al.*, 1995). In the majority of cases it is due to severe metabolic acidosis. It is commonly, though wrongly, ascribed to congestive failure 'secondary' to severe anaemia.

In a study of 24 intensively monitored Kenyan children with severe respiratory distress and acidosis, 16 were severely anaemic (haemoglobin 2·1–4·9 g/dL) (ENGLISH *et al.*, 1996b). Of 22 who had their central venous pressure measured before resuscitation, 13 had a central venous pressure of less than zero and 9 had a central venous pressure between 0 and 5 cm (see Annex 3). Lactate concentrations were significantly higher in the severely anaemic group and plasma creatinine levels were higher in the children with low central venous pressures. Resuscitation with rapid transfusion of blood in the severely anaemic children (10 mL/ kg over 1 h followed by 10 mL/kg over the next 1–4 h) or crystalloid in those with haemoglobin concentration >5 g/dL (10 mL/kg boluses until the central venous pressure stabilized between 0 and 5 cm) led to acute falls in serum lactate and resolution of acidosis in the majority. This was accompanied by marked clinical improvement.

These findings suggest that respiratory distress in the severely anaemic child is commonly due to acidosis resulting from inadequate oxygen delivery to poorly perfused tissues, rather than to congestive cardiac failure. The implications for treatment are important (see p. S1/50).

Hyperpyrexia

High fever is a common feature of falciparum malaria in children, but there is no association between the degree of fever and the presence or likelihood of development of severe malaria. Convulsions in children with malaria may occur at any level of body temperature, but the risk increases at temperatures above 38·5°C (AXTON & SIEBERT, 1982; PATEL, 1971; FAMILUSI & SINNETTE, 1971). Very high temperatures can contribute to altered consciousness or coma. High maternal temperature causes fetal distress in pregnant women with malaria (LOOAREESUWAN *et al.*, 1985b).

Prognostic indices in children

Most complications of malaria are associated with an increased risk of a fatal outcome; some complications are particularly important because they contribute most

to the overall malaria-related mortality in a population. Respiratory distress or altered consciousness predicted 84% of 64 deaths among 1844 Kenyan children admitted to hospital with malaria (MARSH *et al.*, 1995). In a retrospective survey of 2911 children admitted with malaria to hospitals in Thailand, cerebral malaria was associated with the worst prognosis (21 of 96 died), but convulsions in the absence of coma were also associated with an increased risk of dying (4 of 225, compared to 5 of 2590 children without coma or convulsions) (WATTANAGOON *et al.*, 1994). The density of peripheral parasitaemia is an indicator of risk, with mortality increasing greatly at very high levels of parasitaemia. In young children, particularly from areas of high transmission, severe anaemia is the most important manifestation of malaria and mortality rises significantly if the haematocrit is below 13% (haemoglobin 4 g/dL) (LACKRITZ *et al.*, 1993).

Among children with severe malaria, features associated with an increased risk of death include:

- acidosis or increased plasma lactate concentration (TAYLOR *et al.*, 1993; KRISHNA *et al.*, 1994a; MARSH *et al.*, 1995);
- increased cerebrospinal fluid lactate concentration (WHITE *et al.*, 1987a; TAYLOR *et al.*, 1988);
- hypoglycaemia (WHITE *et al.*, 1987a; TAYLOR *et al.*, 1988; MOLYNEUX *et al.*, 1989a; WALKER *et al.*, 1992; KRISHNA *et al.*, 1994a);
- papilloedema and/or retinal oedema (LEWALLEN *et al.*, 1993, 1996)
- more than 20% of parasites in the peripheral blood film contain visible malaria pigment (i.e., they are mature trophozoites or schizonts) (SILAMUT & WHITE, 1993; WALLER *et al.*, 1995);
- depth of coma, witnessed convulsions, age <3 years and parasite density >1 million/μL in cerebral malaria (MOLYNEUX *et al.*, 1989a; WALLER *et al.*, 1995; MABEZA *et al.*, 19950;
- increased plasma concentrations of tumour necrosis factor (TNF) (GRAU *et al.*, 1989b; KWIATKOWSKI *et al.*, 1990);
- more than 5% of peripheral blood neutrophils contain malaria pigment (PHU *et al.*, 1995).

Clinical features of severe falciparum malaria in adults

The shortest pre-patent period (before parasitaemia is evident) for *P. falciparum* following a mosquito bite is 5 d (normal range 5–10 d) and the shortest incubation period (before development of symptoms) is 7 d (normal range 9–14 d, usually 12 d), but this may be greatly prolonged by immunity, chemoprophylaxis or partial chemotherapy. Sixty-five to 95% of non-immune travellers develop their symptoms of falciparum malaria within one month of leaving the malaria-endemic area, but a few present up to one year later. The symptoms and signs of falciparum malaria are non-specific. The illness usually starts with aching of the head, back and limbs, dizziness, malaise, anorexia, vague abdominal pain, nausea, vomiting or mild diarrhoea and with fevers and chills. The classical febrile paroxysms with tertian (alternate day) periodicity are uncommon; an unremittent spiking temperature chart is more usual. Physical signs may include fever, anaemia, jaundice, postural hypotension and tender hepatosplenomegaly (WARRELL, 1983).

In adults, features of severe disease usually appear after 3–7 d of these non-specific feverish symptoms, although there are exceptional reports of non-immune patients dying within 24 h of their first symptom.

During the preparation of the 3 editions of this publication there have been attempts to describe and define more precisely the life-threatening manifestations and complications of severe malaria to help identify more rapidly those patients needing the highest level of care available. Clinical features of severe malaria are listed in Table 1 (p. 2). In many patients several of these conditions exist together or evolve in rapid succession during the first few hours after their admission to hospital.

Cerebral malaria and other neurological abnormalities

In many parts of the world cerebral malaria is the most common clinical presentation and cause of death in adults with severe malaria. In Thailand and Viet Nam about half the cases of severe falciparum malaria had cerebral malaria (TRAN *et al.*, 1996). Among Melanesian adults with severe falciparum malaria in Central Province, Papua New Guinea, only 17% presented with cerebral malaria (LALLOO *et al.*, 1996).

Definition of cerebral malaria. In the past, patients with headache, neck stiffness, drowsiness, delirium, febrile convulsions, focal neurological signs or even behavioural disturbances who were not comatose were often described as having cerebral malaria. In many of the published cases, focal signs and neurological sequelae may well have resulted from other central nervous system infections or vascular disease. In adults, high fever alone without direct involvement of the central nervous system can produce mild impairment of consciousness, variously referred to as delirium, obtundation, obnubilation, confusion and psychosis. To allow comparability of clinical and therapeutic findings, a strict definition of 'cerebral malaria' was recommended (WARRELL *et al.*, 1982).

However, in clinical practice, patients with any degree of impaired consciousness and any other sign of cerebral dysfunction should be treated with the utmost urgency.

This definition requires the presence of unrousable coma using the Glasgow coma scale (TEASDALE & JENNETT, 1974) (Table 5), exclusion of other encephalopathies, especially bacterial meningitis and, if possible, locally prevalent viral encephalitides, and the finding of asexual forms of *P. falciparum* in the blood film. 'Unrousable coma' is defined as a best motor response to noxious stimuli that is 'non-localizing', and a best vocal response that is considered 'incomprehensible' (Table 5) (WARRELL *et al.*, 1982). This level of unconsciousness is chosen because the distinction between obtundation or drowsiness and unrousable coma is clear-cut, whereas minor degrees of unconsciousness are difficult

Table 5. Definition of unrousable coma in adults: modified Glasgow coma scale

	Score[a]
Eyes open	
Spontaneously	4
To speech	3
To pain	2
Never	1
Best verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Best motor response	
Obeys commands	5
Localizes pain	4
Flexion to pain	3
Extension to pain	2
None	1

[a]Total score can range from 3 to 14; 9 or less indicates 'unrousable coma'.

or impossible to separate from the effects of fever alone. In some patients with cerebral malaria the eyes remain open (Fig. 13), and so the eye signs in the Glasgow coma scale are of limited value in such cases. To distinguish cerebral malaria from transient post-ictal coma, unconsciousness should persist for at least 30 min after a convulsion and possibly longer. In the original definition, persistance of coma for 6 h after the seizure was required (WARRELL *et al.*, 1982). Patients falling within this definition of cerebral malaria show the features of diffuse symmetrical encephalopathy. In fatal cases, the diagnosis of cerebral malaria is supported by finding, at autopsy or by post-mortem needle necropsy of the brain (Annex 6), cerebral capillaries and venules packed with parasitized erythrocytes containing pigment, but the absence of these appearances does not exclude cerebral malaria if the patient died after several days of treatment.

Fig. 13. Unrousably comatose patient whose eyes are wide open. (©D. A. Warrell.)

Fig. 14. Woman in Papua New Guinea with cerebral malaria, showing decerebrate rigidity and hyperextension of the neck (©D. G. Lalloo.)

Coma. Cerebral malaria often starts dramatically with a generalized convulsion, followed by persisting unconsciousness. In adults, the level of consciousness is assessed using the Glasgow coma scale (Table 5).

Meningism. Neck rigidity and photophobia are rare symptoms but mild neck stiffness is not uncommon, and hyperextension of the neck may occur in severely ill adults (Fig. 14).

Retinal abnormalities. Papilloedema and exudates are unusual in adults with cerebral malaria, but retinal haemorrhages occur in about 15% of cases (LOOAREESUWAN *et al.*, 1983a).

Other neurological signs. Corneal and eyelash reflexes are usually intact except in deep coma. The pupils are normal. Disorders of conjugate gaze are very common, the usual finding in adults being divergent eyes (Fig. 15)

Fig. 15. Dysconjugate gaze in a woman with cerebral malaria; the optic axes are not parallel in either the vertical or horizontal planes. (©D. A. Warrell.)

with normal oculocephalic ('doll's eye') and oculovestibular (caloric) reflexes (WARRELL, 1983). Convergence spasm, implying an upper brain stem lesion, transient ocular bobbing, horizontal and vertical nystagmus and sixth nerve palsies have been observed rarely.

Forcible jaw closure and tooth grinding (bruxism) (Fig. 9) are common. The jaw jerk may be brisk. A pout reflex is usually elicited indicating frontal release, but other primitive reflexes such as the grasp reflex are almost always absent. The gag reflex is usually preserved. The commonest neurological picture is of a symmetrical upper motor neurone lesion. Muscle tone and tendon reflexes are often increased, but may be variable or reduced. Ankle and sometimes patellar clonus may be elicited and the plantar responses are usually extensor. Abdominal and cremasteric reflexes are invariably absent and are a useful sign for distinguishing hysterical adult patients with fevers of other causes, in whom these reflexes are usually brisk. Various forms of abnormal posturing may be observed, occurring spontaneously or induced or accentuated by noxious stimuli (PLUM & POSNER, 1982). These abnormal motor responses include abnormal flexor response in the arm(s) with extension of the leg(s) — 'decorticate rigidity' (Fig. 16), abnormal extensor responses in arm(s) and leg(s) — 'decerebrate rigidity' (Figs. 14, 17) with or without opisthotonos, and abnormal flexor responses of upper and lower limbs. Sustained upward deviation of the eyes, extension of the neck, pouting and periods of stertorous breathing may occur together (Fig. 18). In the neurological literature, extensor posturing has been described in association with hypoglycaemia (SIEBERT,

Fig. 16. Man with cerebral malaria, showing decorticate rigidity (flexion of the right elbow, extension of the lower limbs). (©D. A. Warrell.)

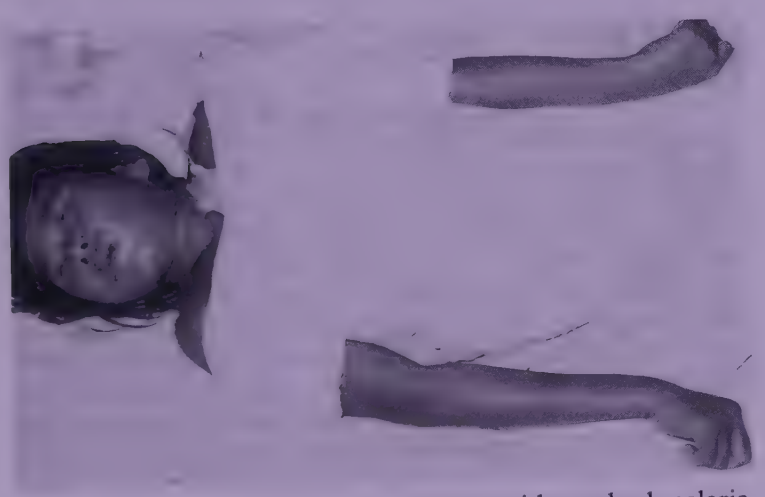

Fig. 17. Decerebrate rigidity in a woman with cerebral malaria complicated by hypoglycaemia. (©D. A. Warrell.)

1985; ANONYMOUS, 1985) but these signs are seen in both hypoglycaemic and normoglycaemic patients with cerebral malaria. Spontaneous movement implies lighter coma and, therefore, a better prognosis than immobility.

Convulsions. The incidence of convulsions in adult Thai and Vietnamese patients has fallen from 50% to less than 20% over the past 10 years without obvious explanation (WHITE, 1995). This might be associated with a reduction in the use of chloroquine for falciparum malaria. Convulsions are usually generalized but Jacksonian type or persistent focal seizures are also observed. A variety of non-specific electroencephalographic abnormalities has been described in both uncomplicated and cerebral malaria (COLLOMB *et al.*, 1977).

Fig. 18. Pouting and sustained upward deviation of the eyes accompanied by stertorous respiration in a man with cerebral malaria complicated by hypoglycaemia. (©D. A. Warrell.)

Brain imaging. Computer tomography (CT) and magnetic resonance imaging (MRI) of the brain in adults with cerebral malaria commonly show evidence of mild cerebral swelling, but oedema is unusual. In Thailand, cerebral oedema was an agonal phenomenon (LOOAREESUWAN *et al.*, 1983b). Focal lesions, suggesting infarction or haemorrhage, have been demonstrated (PHAM-HUNG *et al.*, 1990; MILLAN *et al.*, 1993) and, in a patient with persistent vertical nystagmus, MRI evidence of central pontine myelinolysis was obtained 14 d after admission (KAMPFL *et al.*, 1993). In a patient with focal epilepsy after recovering from cerebral malaria, a small lesion was demonstrated by CT which eventually resolved, as did his symptoms.

A prospective study of MRI imaging of the brain was carried out in Bangkok on 24 adult Thai patients with cerebral malaria (LOOAREESUWAN *et al.*, 1995a). Twenty-two of the patients had no evidence of cerebral oedema, but MRI revealed that brain volume during acute cerebral malaria was slightly greater than during the convalescent phase of the disease. This difference was attributed to an increase in intracerebral blood volume. In 2 fatal cases, in which assisted ventilation had been required, there was gross swelling of the brain in one and foramen magnum herniation in the other.

Brain swelling, cortical infarcts and hyperintense white matter lesions were found in 3 of 12 patients with cerebral malaria (CORDOLIANI *et al.*, 1998). These abnormalities were interpreted as intravascular engorgement oedema and demyelination.

Neurological sequelae. Among Thai adults, more than 95% of survivors of malaria lacked even transient neurological sequelae (WARRELL, 1983). In Viet Nam, a post-malarial neurological syndrome has been described in 22 patients, 3 of them children, all but one of whom had recovered from severe falciparum malaria. Symptoms of either an acute confusional state or psychosis developed in 13, 6 had one or more generalized convulsions, 2 had generalized convulsions followed by a prolonged period of acute confusion, and one developed a cerebellar tremor. In a randomized controlled trial, 4·4% (95% confidence interval [CI] 2·1–7·9) of patients with severe malaria who subsequently developed this syndrome had received mefloquine (MAI *et al.*, 1996). This syndrome has also been seen in Thailand, where there were 3 cases of encephalopathy (psychosis) and 2 cases of tremor (T. M. Davis, personal communication).

Agitation and confusion may develop as the patient recovers consciousness and transient paranoid psychosis or delirium ('brief reactive psychosis') sometimes follows the acute illness (ANDERSON, 1927; BLOCKER *et al.*, 1968) (see below). Other neurological sequelae include cranial nerve lesions, extrapyramidal tremor, ataxia (ABDULLA *et al.*, 1997) and greatly prolonged

coma, but these are unusual (WARRELL, 1983). Focal epilepsy with a transient small cerebral lesion detected by cranial axial tomography was observed in one patient who had recovered from severe but non-cerebral malaria.

Post-infectious and delayed cerebellar ataxia, without impairment of consciousness or other signs of severe malaria, has been described in falciparum malaria, especially in India and Sri Lanka but also, recently, from Sudan (ABDULLA *et al.*, 1997).

Delayed cerbellar ataxia. Three or 4 weeks after developing transient fever attributable to falciparum malaria, patients present with unsteadiness of gait and ataxia of the upper limbs, vertigo, dysarthria and headache. On examination there is ataxia of gait, intention tremor, dysmetria, dysdiadochokinesis, nystagmus and cerebellar dysarthria. Symptoms progress for up to 2 weeks but completely resolve 3–16 weeks (median=10) after their onset (SENANAYAKE, 1987).

'*Malarial psychoses*'. It is doubtful whether there is a specific 'malarial psychosis'. However, there are many references, especially in the older literature, to a variety of psychiatric manifestations attributed to malaria, both as the presenting feature of an acute attack of malaria and as a sequel, in convalescence, to an episode of severe or otherwise uncomplicated malaria. Limitations of many of these reports are failures to confirm the diagnosis of malaria and to exclude other causes of the psychiatric symptoms, such as antimalarial drugs (e.g., mepacrine, chloroquine [AKHTAR & MUKHERJEE, 1993] and mefloquine [WEINKE *et al.*, 1991; AKHTAR & MUKHERJEE, 1993; LUXEMBURGER *et al.*, 1994; MAI *et al.*, 1996]). Other factors implicated in 'malarial psychosis' include alcohol, alcohol withdrawal, narcotics, stresses associated with life or military service in tropical countries, and exacerbation of pre-existing functional psychoses (BLOCKER *et al.*, 1968). Psychiatric features include apathy, amnesia, depression, atypical depression, acute psychosis, personality change, paranoid psychosis, and delusions, such as belief that family members have been killed (BLOCKER *et al.*, 1968; PRAKASH & STEIN, 1990; DUGBARTEY *et al.*, 1998). Brief reactive psychoses (LIPOWSKI, 1980) have been observed in patients recovering from cerebral malaria (WARRELL *et al.*, 1982; MAI *et al.*, 1996). These symptoms rarely last for more than a few days, in contrast to those attributable to functional psychoses.

Anaemia

Anaemia is an inevitable consequence of severe malaria. On admission, 10% of adults are anaemic (haemoglobin <7g/dL, packed cell volume <20%) and, in Thailand, haematocrits fell below 20% in approximately 30% of adult patients in one study (PHILLIPS *et al.*, 1986a). The degree of anaemia correlated with parasitaemia, schizontaemia, and serum total bilirubin and creatinine concentrations.

Haemoglobinuria and blackwater fever

Classical descriptions of blackwater fever (BARRATT & YORKE, 1910; BLACKIE, 1944; MAEGRAITH, 1948, 1952) mention severe intravascular haemolysis with haemoglobinuria in patients with severe manifestations of *P. falciparum* infection, such as renal failure, hypotension and coma, but scanty or absent parasitaemia and mild or absent fever (Fig. 19). The typical patient was an expatriate European who had lived in the endemic area for several months or longer, had had previous attacks of malaria, and was taking quinine in an irregular fashion for prophylaxis and treatment. Symptoms associated with what was initially a typical attack of malaria included loin pain, vomiting, diarrhoea and polyuria followed by oliguria and passage of mahogany-coloured, or even black, urine. Signs included tender hepatosplenomegaly, profound anaemia and jaundice. The exaggerated haemolytic response in the absence of hyperparasitaemia was attributed to immune lysis of quinine-sensitized erythrocytes (BRUCE-CHWATT, 1987).

Fig. 19. Patient severely ill with cerebral malaria and haemoglobinuria (there was no evidence of glucose 6-phosphate dehydrogenase deficiency or other inherited erythrocyte abnormality). (©R. E. Phillips.)

In the 1960s and 1970s, haemoglobinuria was observed less frequently, associated with increasing use of chloroquine. Intravascular haemolysis with haemoglobinuria has also been observed in Africa among patients who had repeatedly used quinine or halofantrine to treat febrile episodes (VACHON *et al.*, 1992; MOJON *et al.*, 1994). Much of the older literature dealing with indigenous populations must be re-evaluated now that glucose-6-phosphate dehydrogenase (G-6PD) deficiency (GILLES & IKEME, 1960) and other erythrocyte enzyme deficiencies have been recognized. These days, the majority of patients with haemoglobinuria in tropical countries are suffering from the oxidant effects of antimalarial drugs on erythrocytes deficient in G-6PD or other enzymes. However, more than half of 50 patients with fever and haemoglobinuria studied in Viet Nam, one-third of whom had malaria, had ingested quinine, a non-oxidant drug (CHAU *et al.*, 1996). In these patients, vomiting, loin pain and passage of black/red ('Coca-Cola' coloured) urine were common symptoms. Patients were usually very pale with a characteristic slate grey skin coloration. The majority of patients did not have acute renal failure (CHAU *et al.*, 1996). Self treatment with quinine, often in inadequate doses, was until recently a common practice in Viet Nam, as in the days when blackwater fever was first described in West Africa. During the 1980s, large supplies of 'chloroprima' (a combination of chloroquine and primaquine used for prophylaxis) were available in the villages and used for

self-treatment of fever. In a large controlled trial comparing artemether and quinine in Vietnamese adults with severe falciparum malaria, 7 artemether recipients (2%) and 4 quinine recipients (1%) passed black urine (TRAN *et al.*, 1996).

Jaundice and hepatic dysfunction

Jaundice is common in adult patients with malaria (WARRELL & FRANCIS, 1990). In a study of 390 patients with acute falciparum malaria in Thailand, 124 were clinically jaundiced (total serum bilirubin ≥3 mg/dL) (WILAIRATANA *et al.*, 1994). Among the jaundiced patients, hyperbilirubinaemia was predominantly unconjugated. Jaundice was associated with cerebral malaria, acute renal failure, pulmonary oedema, shock and other severe complications. In Vietnamese adults, 63% of those with acute renal failure were jaundiced, compared to 20% of those without renal failure (TRANG *et al.*, 1992). In eastern Thailand, 19% of all patients with falciparum malaria were jaundiced, but 45% of those with parasitaemias of more than 100 000/μL were jaundiced (HALL *et al.*, 1975b). Apart from jaundice, signs of hepatic dysfunction are unusual, although functional disturbances implied by altered handling of antimalarial drugs are common. Clinical signs of liver failure with hepatic encephalopathy (such as asterixis or 'liver flap') are never seen unless there is concomitant viral hepatitis. Tender enlargement of the liver and spleen are common findings in all human malarias, especially in young children and non-immune adults.

Mild jaundice may result from haemolysis alone, but very high bilirubin concentrations indicate hepatocyte dysfunction (BARTELLONI *et al.*, 1967; GLOR, 1969). In these cases, concentrations of unconjugated (Van den Bergh indirect) and conjugated bilirubin are increased. Some patients with blackwater fever show evidence of cholestasis.

Low and falling serum albumin level is an important index of hepatic dysfunction. Concentrations of aspartate and alanine aminotransferases may be increased up to tenfold but never to the level seen in viral hepatitis; 5′nucleotidase and γ glutamyl transpeptidase concentrations may also be moderately elevated. Prothrombin time may be moderately prolonged. Other abnormalities include lactic acidosis, hypoglycaemia and changes in levels of triglycerides, phospholipids, free fatty acids, cholesterol, esterified cholesterol and non-esterified fatty acids (see p. S1/30).

Haemostatic abnormalities, thrombocytopenia

Fewer than 10% of adult Thai patients with cerebral malaria showed clinically evident bleeding tendency with associated features of disseminated intravascular coagulation (PHILLIPS *et al.*, 1986a), but laboratory evidence of activated coagulation was common. Bleeding gums, epistaxis, haematemesis, petechiae, and subconjunctival haemorrhages were seen (Fig. 20). Bleeding usually occurs in patients with renal, pulmonary or hepatic complications and is associated with hyperparasitaemia, severe anaemia, thrombocytopenia and coagulopathy (STONE *et al.*, 1972; PUNYAGUPTA *et al.*, 1974). In these series of patients, the incidence of bleeding ranged from 10% to 25% (SRICHAIKUL, 1993), but these incidences are misleadingly high for patients with severe malaria as a whole. Gastrointestinal haemorrhage is particularly associated with corticosteroid therapy (WARRELL *et al.*, 1982; HOFFMAN *et al.*, 1988).

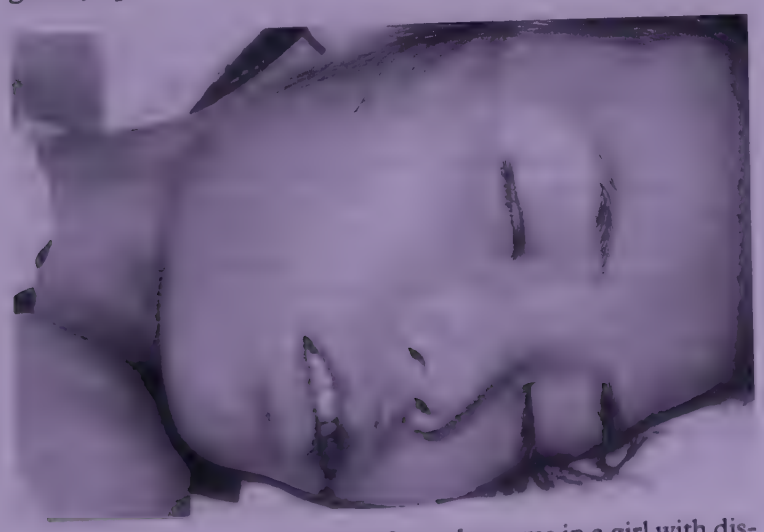

Fig. 20. Spontaneous bleeding from the gums in a girl with disseminated intravascular coagulation complicating cerebral malaria. (©D. A. Warrell.)

Thrombocytopenia is a common feature of falciparum and vivax malarias, whether mild or severe, but profound thrombocytopenia (<20 000/μL) is more common in severe falciparum malaria (HORSTMANN *et al.*, 1981). Altered platelet function has also been described (SRICHAIKUL, 1993). Thrombocytopenia is not related to other measures of coagulation (prothrombin time, partial thromboplastin time) or to plasma fibrinogen concentrations. It does not, in itself, indicate disseminated intravascular coagulation, and in most cases is unaccompanied by bleeding. Laboratory tests of coagulation are usually normal. Plasma fibrinogen is in the high normal or slightly elevated range, although its breakdown is accelerated (DEVAKUL *et al.*, 1966). Fibrin degradation products are usually slightly elevated (REID & NKRUMAH, 1972).

Renal dysfunction

Acute renal failure is a common complication of severe falciparum malaria and is often lethal (HABTE, 1990; HIEN *et al.*, 1990). It occurs almost exclusively in adults and older children (WEBER *et al.*, 1991).

Malarial acute renal failure may be defined as a serum creatinine concentration >265 μmol/L (3 mg/dL) with 24 h urine output <400 mL, in spite of rehydration, in patients who have asexual forms of *P. falciparum* in their peripheral blood film. It is a particular complication in patients with delayed referral and/or delayed treatment. It is more common in males, but this probably reflects the overall higher incidence of falciparum malaria in men in areas of low or unstable transmission.

There are 2 categories of patients with acute renal failure: those with acute severe malaria and multiple organ involvement (which has a poor prognosis) and those patients whose acute infection has been treated successfully with antimalarial drugs but who still develop renal failure (whose prognosis is good, provided that dialysis is available). The latter group tends to be more anaemic and to have a higher serum creatinine concentration on admission, reflecting longer duration of illness before referral (TRANG *et al.*, 1992). In a prospective series of more than 500 adult patients with severe and complicated malaria in Viet Nam, approximately 50% had biochemical evidence of renal involvement (serum creatinine >2 mg/dL). These patients had a significantly higher incidence of jaundice, hypoglycaemia and hyperkalaemia than those who had a normal serum creatinine level. However, only 30% of patients in this series fulfilled the stricter WHO criteria for acute renal failure, and half of them needed dialysis (Tran Tin Hien, personal communication). Acute renal failure in malaria is usually oliguric (<400 mL/d) or anuric (<50 mL/d), but urine output may also be normal or increased. In another study of dialysed patients in Viet Nam, 25% had normal 24 h urine output but had steadily rising levels of serum creatinine and blood urea, and hyperkalaemia (Tran Tin Hien, personal communication). Oliguria alone will not identify all cases of acute renal failure. Daily measurement of serum creatinine concentration is the most important investigation.

In 30% of adult patients with cerebral malaria in Thailand, serum creatinine rose above 2 mg% and blood urea nitrogen rose above 40 mg% (PHILLIPS *et al.*, 1984). These patients had a higher incidence of hypoglycaemia and jaundice, and coma was significantly

prolonged. Pulmonary oedema was common in this series, and more than 50% of Stone's (1972) series of patients with renal failure died with this complication. Overall mortality among those with renal failure was 45%, compared with 10% in those without.

Fluid balance

Many untreated patients with severe falciparum malaria are clinically hypovolaemic (low jugular venous pressure, postural hypotension, oliguria with high urine specific gravity) and dehydrated (reduced skin turgor) on admission.

Hyponatraemia

Mild hyponatraemia (serum sodium 125–135 mmol/L) is relatively common in falciparum malaria (MILLER, L. H. *et al.*, 1967; OGUNYE & GBADEBO, 1981; FRYATT *et al.*, 1989; HOLST *et al.*, 1994) and is often accompanied by mildly reduced plasma osmolality. Salt depletion through prolonged sweating or dilution from administration of intravenous dextrose solutions contribute to it.

Pulmonary oedema

This is a grave and usually fatal manifestation of severe falciparum malaria in adults, which may develop suddenly after one or 2 days' treatment (Figs 21, 22). Some cases show evidence of fluid overload, with raised central venous or pulmonary artery wedge pressures and grossly positive fluid balance BROOKS *et al.*, 1968; HALL *et al.*, 1975a; HALL, 1976, 1977; WHITE, 1986).

Fig. 21. Acute pulmonary oedema developing immediately after delivery in a woman with severe falciparum malaria. (©Sornchai Looareesuwan.)

Fig. 22. Radiographic appearance of acute pulmonary oedema resembling adult respiratory distress syndrome in a patient with cerebral malaria. (©D. A. Warrell.)

Other patients develop pulmonary oedema with normal or negative fluid balance and with normal or reduced pulmonary wedge pressure; this condition resembles adult respiratory distress syndrome (FEIN *et al.*, 1978; MARTELL *et al.*, 1979; BLANLEOIL *et al.*, 1980; MARTIN *et al.*, 1982; JAMES, 1985; WHITE, 1986; WARRELL, 1987a). Hyperparasitaemia, renal failure and pregnancy are predisposing factors. Hypoglycaemia and metabolic acidosis are commonly associated. Pulmonary oedema may also occur in vivax malaria.

The first indication of impending pulmonary oedema is usually an increase in the respiratory rate which precedes the development of other chest signs. Without good facilities for emergency radiography it may be difficult to differentiate acute pulmonary oedema from aspiration bronchopneumonia and metabolic acidosis, although, in the last of these, auscultation of the chest is usually normal (Fig. 22). Although pulmonary oedema may develop at any stage of the acute illness, it tends to occur later than the other acute manifestations of malaria (BROOKS *et al.*, 1968). Central venous and pulmonary artery occlusion pressure are usually normal, indicating that the cause of the oedema is an increase in the pulmonary capillary permeability. Hypoxia may cause convulsions and deterioration in the level of consciousness and the patient may die within a few hours.

Cardiovascular abnormalities, shock, 'algid malaria'

The blood pressure of patients with malaria is usually at the lower end of the normal range. Severe hypotension (systolic blood pressure <80 mm Hg [10·7 kPa] in adults in the supine position) with features of circulatory failure (cold, clammy, cyanotic skin, constricted peripheral veins, etc.) is seen in patients with pulmonary oedema, metabolic acidosis, Gram-negative septicaemia (see below) and following massive gastrointestinal haemorrhage or splenic rupture (Fig. 23). Dehydration may also contribute to hypotension, and patients may

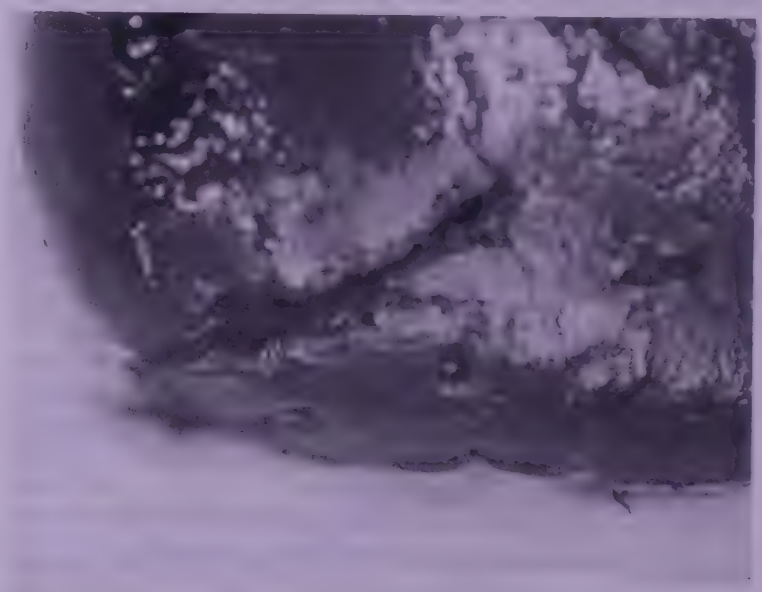

Fig. 23. Ruptured spleen removed from a patient with severe malaria. (©J.-E. Touze.)

be admitted severely dehydrated, hypotensive and oliguric, having endured high fever and inadequate fluid intake for several days.

Myocardial failure and cardiac arrhythmias are very rarely observed in severe malaria, despite the sequestration of parasitized erythrocytes in the myocardial vessels and the marked cardiac effects of many antimalarial drugs (BETHEL *et al.*, 1996).

In Thailand and elsewhere, the clinical picture of 'algid malaria' resembled that of septic shock and was usually associated with demonstrable bacteraemia (see p. S1/17).

Acid–base disturbances

Acidotic breathing (hyperventilation, Kussmaul's

respiration) may develop in severely ill patients who are shocked, develop lactic acidosis or are in renal failure (see p. S1/10).

Gastrointestinal symptoms

Nausea, vomiting (20–30% of patients), abdominal pain, which may be colicky and severe, and diarrhoea (10–20% of patients) which may be watery but does not contain blood or pus cells, occur in adults with severe malaria. It is of great practical importance for a patient who consistently vomits tablets to be transferred to a place where parenteral treatment can be given, unless suppositories are available.

Hypoglycaemia

Hypoglycaemia is now well recognized as a complication of falciparum malaria and its treatment. Usually it is not suspected clinically because the patient is suffering from severe falciparum malaria. In conscious patients, hypoglycaemia may present with classical symptoms of anxiety, breathlessness, a feeling of coldness, tachycardia, and light-headedness and signs of autonomic overactivity (sweating, or 'goose-flesh'). More severe signs include coma, deteriorating consciousness, abnormal posturing (decerebrate or decorticate rigidity, muscle spasms, pouting, stertorous breathing and opisthotonos) and generalized convulsions. The diagnosis of hypoglycaemia may be overlooked because all these clinical features are also typical of severe malaria *per se*. Furthermore, in severe malaria many of the usual diagnostic features of hypoglycaemia may be absent.

Sweating is an inconstant sign, the pupils are frequently not dilated, the breathing may be cyclical or stertorous and deep, and there may be abnormal posturing of the arms and legs. There is usually a deterioration in the level of consciousness. In Thai adults, treatment with intravenous 50% glucose usually resulted in an improvement in the respiratory pattern and often there was a lightening of coma.

Hypoglycaemia complicates malaria in 3 clinical settings which may overlap: in patients given quinine or quinidine, in pregnant women, and in patients with severe disease — especially young children (see pp. S1/8–S1/9).

Hypoglycaemia related to quinine/quinidine treatment. Quinine-induced hyperinsulinaemia is a common cause of hypoglycaemia, particularly in pregnant women and in children (WHITE *et al.*, 1983a; LOOAREESUWAN *et al.*, 1985a; NARULA *et al.*, 1985; MBELEPE *et al.*, 1986; OKITOLONDA *et al.*, 1987; DAS *et al.*, 1988). Quinidine is the only other antimalarial drug known to be capable of stimulating insulin secretion *in vitro* and in patients (PHILLIPS *et al.*, 1986b). Quinine may induce hyperinsulinaemic hypoglycaemia in conditions other than malaria, for example when used for the treatment of nocturnal cramps (HARATS *et al.*, 1984).

Hypoglycaemia in pregnant women. This is discussed below (p. S1/19).

Hypoglycaemia in patients with severe disease. Hypoglycaemia is associated with severe malaria in adults and children (see above) and has a bad prognosis. Hypoglycaemia has been found in adults with severe manifestations such as cerebral malaria, severe anaemia, jaundice, high parasitaemia and lactic acidosis at a time when their plasma insulin levels were appropriately low, before quinine treatment had begun (WHITE *et al.*, 1983a; KIIRE, 1986).

Other metabolic abnormalities

Hypocalcaemia. Hypocalcaemia has been observed in patients with severe falciparum malaria (PETITHORY *et al.*, 1983), but in some cases this was explained by an associated hypoalbuminaemia, an almost universal finding in these patients. In Thailand, a cross-sectional study of 172 adults with acute falciparum malaria discovered that 35·5% had mild asymptomatic hypocalcaemia (1·79–2·11 mmol/L corrected). There was no difference between severe and uncomplicated cases. However, among 10 cases studied prospectively, hypocalcaemia was found in 6, associated with inappropriately low intact parathormone concentrations in the serum (<5·0 pmol/L) (DAVIS *et al.*, 1991). Despite malaria-associated haemolysis, hypophosphataemia (<0·80 mmol/L) was found in 43% of the 172 patients and hyperphosphataemia (>1·34 mmol/L) in 8·7%. Severe hypophosphataemia (<0·30 mmol/L) was also found in 11 patients with severe malaria by DAVIS *et al.* (1991).

Hypophosphataemia. Severe hypophosphataemia could contribute to disturbances of cerebral, leucocyte and platelet function and to haemolysis, and is exaggerated by administration of glucose and by quinine-induced hyperinsulinaemia.

Other conditions. Some alterations in lipid metabolism, reflected by hyperphospholipidaemia, hyperphospholipase-A_2aemia, hypertriglyceridaemia or hypocholesterolaemia have been found in Caucasian patients with imported malaria in France (M. Danis, personal communication) and Sweden (NILSSON-EHLE & NILSSON-EHLE, 1990).

Complicating and associated infections

Other severe and life-threatening infections may arise in patients with severe falciparum malaria. In some cases there are complicating infections: e.g., aspiration bronchopneumonia in patients who have had generalized convulsions; urinary tract infections in patients with indwelling urethral catheters; infected decubitus ulcers in patients with prolonged coma; and infection around intravenous cannulae.

Gram-negative septicaemia may occasionally coexist with severe falciparum malaria without an evident focus. These patients appear unusually vulnerable to infection. In Viet Nam, only one case of Gram-negative septicaemia was detected among 500 patients on admission. In 10 cases, 5 of them fatal, among 175 with strictly defined cerebral malaria in Thailand (WARRELL *et al.*, 1982; D. A. Warrell, unpublished observations), Gram-negative bacteria were cultured from the blood (*Escherichia coli* in 3, *Pseudomonas aeruginosa* in one, and uncharacterized bacteria in 6). Four cases were explained by urinary tract infections associated with indwelling urethral catheters or aspiration pneumonia. GOODALL (1981) reported *E. coli* and *Clostridium perfringens* septicaemias in 2 fatal cases. *E. coli* and *P. aeruginosa* septicaemias have been described in 2 patients in Denmark (BYGBJERG & LANNG, 1982; KHARAZMI *et al.*, 1987). Other associated infections include streptococcal septicaemia (LUCHT *et al.*, 1986), listeriosis (VON SONNENBURG *et al.*, 1986), legionnaire's disease (LUCHT *et al.*, 1986), salmonella and *Pasteurella multocida* septicaemia (WALLER *et al.*, 1995). In African children, salmonella infections may complicate falciparum malaria (MABEY *et al.*, 1987; K. Marsh *et al.*, personal communication). Thus, septicaemia must always be considered and excluded or treated in severely ill patients with malarial parasitaemia.

Peripheral leucocytosis

Peripheral neutrophil leucocytosis has been observed in severe falciparum malaria, even in the absence of detectable secondary bacterial infection. It is associated with a poor prognosis (WARRELL *et al.*, 1982; MOLYNEUX *et al.*, 1989b). Leucopenia is common in some populations (STRONG, 1944). Leucaemoid reactions have been reported (IRVING *et al.*, 1987; STEIN, 1987). In cerebral malaria, corticosteroid therapy was not followed by a significant increase in leucocyte count (WARRELL *et al.*, 1982).

Rhabdomyolysis

Generalized myalgia, myoglobinuria and histological evidence of inflammatory skeletal muscle necrosis were

reported in a Sri Lankan adult with falciparum malaria (DE SILVA *et al.*, 1988), but skeletal muscle damage sufficient to cause renal failure appears to be rare. It has also been reported in African Children (MILLER, K. D. *et al.*, 1989b).

Prognostic indices in adults

The prognosis in severe malaria is determined by the number of vital organ systems that are involved and the severity of their dysfunction.

Clinical indicators

Any degree of central nervous system dysfunction carries an increased risk of mortality. Confusion, agitation and obtundation are all risk factors. Unrousable coma or cerebral malaria has an approximate 20% mortality rate in adults and 15% in children. Marked, often violent, agitation in young adults may precede rapid deterioration. Convulsions often progress to coma and, even with rapid recovery, define a group at increased risk in areas of low or unstable transmission (WATTANAGOON *et al.*, 1994). Although cerebral malaria is undoubtedly the most important severe manifestation of malaria, patients of all ages may die without cerebral involvement.

In recent years in Viet Nam and Thailand, the clinical pattern of severe malaria has changed. Over a decade ago cerebral malaria was the predominant manifestation of severe malaria, whereas today the combination of jaundice and renal failure is more common. The incidence of convulsions in cerebral malaria has also declined. Renal impairment is an indicator of severity, and the prognosis of acute renal failure is worsened by coexistent jaundice (TRANG *et al.*, 1992). The prognosis of cerebral malaria is worsened considerably if there is also renal failure. The signs of acidosis or uraemia represent a late stage in the progression of the disease. Oliguria or anuria is usually present, but may not have been recorded. Measurement of blood urea or creatinine is often the only method of diagnosis. In adults, severe anaemia is less prominent. The prognosis of severe anaemia in the absence of other severe manifestations of malaria is good. Recent studies have emphasized the prognostic importance of acidosis, reflected as acidotic breathing, or measured as arterial pH, base deficit, plasma bicarbonate concentration, or as arterial, venous, or cerebrospinal fluid lactate concentration (WHITE *et al.*, 1985; TAYLOR *et al.*, 1993; KRISHNA *et al.*, 1994a; MARSH *et al.*, 1995; WALLER *et al.*, 1995). In children respiratory distress or rapid deep laboured breathing (reflecting acidosis, pulmonary oedema, or aspiration pneumonia) identifies a subgroup at high risk of dying independent of cerebral malaria (MARSH *et al.*, 1995). This is usually a late sign in adults. The time to death from the onset of acidotic breathing is even shorter in children. Significant bleeding is associated with an increased risk of dying. Jaundice has a poor prognosis only if combined with other evidence of severe disease.

Laboratory indices

Laboratory indicators of poor prognosis observed in Thai adults with cerebral malaria studied nearly 20 years ago (WARRELL *et al.*, 1982) included hyperparasitaemia (more than 5% erythrocytes parasitized or more than 250 000 parasites/μL); peripheral schizontaemia; peripheral leucocytosis (>12 000/μL); high cerebrospinal fluid lactate and low cerebrospinal fluid glucose levels (WHITE *et al.*, 1985); low antithrombin III levels; creatinine >265 μmol/L (>3·0 mg/dL); and blood urea nitrogen >21·4 mmol/L (>60 mg/dL); packed cell volume <20% or haemoglobin <4·4 mmol/L (<7·1 g/dL); blood glucose <2·2 mmol/L (<40 mg/dL) (WHITE *et al.*, 1983a); raised venous lactate (>6 mmol/L) (WHITE *et al.*, 1985); and more than three-fold elevated serum enzyme concentrations (aspartate and alanine aminotransferases). More recent studies have confirmed these findings, and emphasized the usefulness of venous lactate or bicarbonate concentrations as prognostic indicators.

The prognostic value of the parasite count, as a measure of parasite burden, depends on the age and degree of background immunity of the patient. The classical work of Field in peninsular Malaya (an area of relatively low seasonal transmission) first characterized the relationship between parasitaemia and prognosis (FIELD & NIVEN, 1937; FIELD, 1949). There was a correlation between parasite counts and prognosis, with a significant increase in mortality with parasitaemias over 2%. In Field's original series, a parasitaemia over 500 000/μL was associated with >50% mortality. This loose relationship differs according to age and intensity of malaria transmission. In areas of higher transmission, the mortality associated with this parasitaemia would be considerably lower. In non-immune subjects, parasitaemias over 4% are considered sufficiently dangerous to warrant treatment for severe falciparum malaria (LUXEMBURGER *et al.*, 1995). In endemic areas the threshold is higher. The prognostic value of the parasite count may be improved considerably by assessing the stage of parasite development in the peripheral blood film; at any parasitaemia prognosis worsens if there is a predominance of more mature parasite stages. In general, if more than 50% of the peripheral blood parasites are at the tiny ring stage (when the diameter of the nucleus is less than half the diameter of the rim of cytoplasm) the prognosis is relatively good, whereas if more than 20% of the parasites contain visible pigment (i.e., are mature trophozoites or schizonts) the prognosis is relatively bad (SILAMUT & WHITE, 1993). A recent study from Viet Nam has shown that assessment of peripheral blood polymorphonuclear leucocyte pigment is an extremely rapid and relatively accurate prognostic index (PHU *et al.*, 1995). In a series of 300 adults with severe malaria, the prognosis worsened considerably if more than 5% of peripheral blood polymorphonuclear leucocytes contained visible pigment.

Dangerous antecedent factors for the development of severe falciparum malaria include splenectomy, pregnancy, corticosteroid or cytotoxic drug use, immunosuppression, lack of previous malaria exposure and, to a much lesser extent, lapsed immunity.

Clinical features of severe falciparum malaria in pregnant women

The effects of *P. falciparum* infection in a pregnant woman depend largely on the epidemiological setting.

In areas of low transmission

In areas of low transmission, falciparum malaria is an important cause of maternal mortality. The case-fatality rate of severe malaria is greater in pregnancy than in non-pregnant women. Malaria may also cause abortion, still birth, premature delivery and low birth weight (MENON, 1972). NOSTEN *et al.* (1991) observed 1358 Karen women (on the Thai–Myanmar border) weekly throughout most of the second half of pregnancy. Despite prompt treatment of parasitaemia (often presymptomatic), birth weights of babies born to mothers with *P. falciparum* infection were significantly reduced, especially in first pregnancies and, to a decreasing extent, in later pregnancies. In the same area, maternal anaemia at term, which was statistically associated with maternal malaria, was a predictor of increased infant mortality (NOSTEN *et al.*, 1994).

In residents of low transmission areas and in travellers from non-endemic areas, pregnancy increases the risk that a *P. falciparum* infection will develop into severe disease. In these settings, complicated malaria in the pregnant woman may consist of any of the clinical syndromes seen in adults (see pp. S1/11–S1/18). Two complications to which pregnant women are particularly susceptible are hypoglycaemia and pulmonary oedema.

Hypoglycaemia. Hypoglycaemia was identified before the start of quinine treatment in 7 of 12 pregnant women with severe malaria (LOOAREESUWAN *et al.*, 1985a), and developed during the course of quinine therapy in 50% of pregnant women with cerebral malaria (WHITE *et al.*, 1983a).

In untreated patients there is a statistical association of hypoglycaemia with hyperparasitaemia and lactic acidosis; hypoglycaemia may, however, be an isolated complication. It may be asymptomatic, or may present with sweating, altered consciousness or convulsions. There may be associated fetal bradycardia or other signs of fetal distress. There is a danger that the diagnosis may be missed because the clinical features resemble those of complicated malaria.

Quinine-treated patients who are in the second or third trimesters of pregnancy are at high risk of hypoglycaemia, whether they are suffering from severe or mild malaria. Asymptomatic hypoglycaemia may be unrecognized, and cerebral effects may be mistakenly attributed to the malarial infection. Hypoglycaemia may recur after correction by intravenous glucose therapy. The susceptibility to quinine-induced hypoglycaemia persists for several days into the post-partum period after symptoms of malaria have resolved (D. A. Warrell & N. J. White, unpublished observation).

Acute pulmonary oedema. Pregnant patients with severe falciparum malaria are particularly prone to develop acute pulmonary oedema. This may be present on admission or develop suddenly several days after admission to hospital. It commonly develops immediately after delivery, and may occur at any time in the first week post-partum (Tran Tin Hien, personal communication).

Premature labour. Falciparum malaria in non-immune subjects commonly induces uterine contractions and premature labour. The frequency and intensity of the contractions appear to be related to the height of fever (LOOAREESUWAN *et al.*, 1985a). Fetal distress is common but frequently not diagnosed. The fetal prognosis in premature labour is poor, particularly in severe disease. Despite control of the infection and prevention of labour, intrauterine growth may be temporarily retarded.

In areas of high transmission

In areas of high transmission, malarial infection is common, but severe or complicated disease — with the possible exception of severe anaemia — is uncommon, and malaria is unusual as a direct cause of maternal death. However, in Mozambique, between 1989 and 1993, 15·5% of maternal deaths were directly attributable to malaria and 19·7% of the mothers who died were found to have *P. falciparum* parasitaemia before death (GRANJA *et al.*, 1998). Pregnant women are more likely to be parasitaemic and to have higher parasitaemias than non-pregnant women of the same age (BRABIN, 1983; GARIN *et al.*, 1985; STEKETEE & WIRIMA, 1996). The increased incidence and density of parasitaemia are maximal in the second trimester, and are most evident in first and second pregnancies. Placental parasitaemia is common, is most intense in primigravidae, and frequently occurs in patients without peripheral parasitaemia (MCGREGOR *et al.*, 1983; NYIRJESY *et al.*, 1983).

In these settings, 'severe' effects of malaria appear to be limited to the following 2 clinical consequences of the infection.

Maternal anaemia. In malaria-endemic areas anaemia is common in pregnancy and has many possible causes (FLEMING, 1989). In areas of high transmission, several studies have shown that malaria plays an important role in the determination of anaemia in primigravidae (GILLES *et al.*, 1969; JILLY, 1969; BRABIN, 1983; MCGREGOR, 1984; MATTEELLI *et al.*, 1994; SHULMAN *et al.*, 1996). The contribution of malaria to anaemia in primigravidae may differ in different circumstances. Thus, in some areas, malarial anaemia and iron deficiency not uncommonly co-exist.

Low birth weight. Placental malaria is associated with low birth weight (BRUCE-CHWATT, 1952; MCGREGOR *et al.*, 1983). In many studies, the reduction of mean birth weight associated with placental malaria has been greatest in first pregnancies, decreasing with increasing parity (BRABIN, 1983; MCGREGOR *et al.*, 1983). In areas of low or unstable transmission, both falciparum and vivax malaria are associated with a reduction in birth weight, not only in the first pregnancy but also in the second, and sometimes third, pregnancies (NOSTEN *et al.*, 1991; F. Nosten, unpublished observations). The average reduction in birth weight of babies born to primigravidae is approximately 170 g, resulting in an increased proportion of babies with low birth weight (<2·5 kg). Malaria-associated low birth weight is usually due to intra-uterine growth retardation rather than to premature delivery (STEKETEE & WIRIMA, 1996).

The clinical importance of this phenomenon is uncertain. In a study of over 4220 pregnant women in rural Malawi, where placental malaria was associated with low birth weight in all parity groups, no association could be shown between malaria infection and mid-trimester fetal loss, perinatal mortality or neonatal mortality (WIRIMA, 1996). In this study the infant mortality rate was 163 per 1000 live births; low birth weight babies were in general at increased risk of death during infancy, so it is likely that maternal malaria made some indirect contribution to infant mortality.

An association between placental parasitaemia and low birth weight could not be found in a study of 83 pregnant women in Papua New Guinea, of whom 22 were primigravidae, 41% of the latter having (low density) placental parasitaemia (DESOWITZ & ALPERS, 1992). Much larger numbers are required in order to establish whether this is a real geographical difference from the picture in Africa.

In a study of 2608 Malawian women, placental malaria was associated with increased infant mortality associated with human immunodeficiency virus (HIV) infection (BLOLAND *et al.*, 1995). The possibility that placental malaria may promote mother-to-child transmission of HIV remains to be tested. The prevalence of parasitaemia was highest in HIV seropositive than HIV seronegative pregnant women and infant mortality was twice as high in the HIV seropositive women with malaria than in HIV seronegative women with malaria (F. H. Verhoeff, personal communication).

Placental parasitaemia may impair the transfer of maternal antibodies to the fetus. Neonatal tetanus may occur because of inadequate maternal immunization, but the possibility that placental malaria may contribute has been raised by a study of maternal and cord blood tetanus antibody titres in 224 Papua New Guinea women (BRAIR *et al.*, 1994). Cord:maternal tetanus antibody titre ratios were reduced in proportion to the intensity of placental *P. falciparum* parasitaemia, and about 10% of babies with heavily malaria-infected placentae had cord tetanus antibody titres below the level usually considered to be protective, despite adequate maternal levels. In rural Malawi, 15 of 184 neonatal deaths met the WHO criteria for neonatal tetanus. Most of the mothers of these infants had a history of one or 2 tetanus toxoid immunizations during pregnancy. Placental malaria was common in this area, although its possible contribution to neonatal tetanus was not examined in this study (STEKETEE & WIRIMA, 1996).

Congenital malaria. In endemic areas, despite a high incidence of maternal parasitaemia and placental malarial infections, symptomatic malaria in the neonate is rare (COVELL, 1950; LOGIE & MCGREGOR, 1970). Nevertheless parasites are commonly present in umbilical cord blood — cord parasitaemia was identified in 123 of 1732 deliveries (7%) in Malawi, and in 87% of 23 babies born to mothers with peripheral parasitaemia levels above 10 000/μL (STEKETEE & WIRIMA, 1996). Cord blood parasitaemia was a significant predictor of

low birth weight. The rate of neonatal peripheral parasitaemia is lower than the rate of cord parasitaemia, and parasitaemia disappears within a few days of birth (NYIRJESY *et al.*, 1993).

Infants born to non-immune mothers who have malaria at the time of parturition may develop parasitaemia and illness in the first few weeks of life (QUINN *et al.*, 1982). *P. falciparum* was responsible for 64% of 107 cases of congenital malaria reviewed by COVELL (1950), but for only 6% of 49 cases occurring in the USA between 1955 and 1990, most of which were due to *P. vivax* (HULBERT, 1992). Clinical features, which usually appear between the second and eighth weeks of life, include fever, anorexia, lethargy, anaemia and hepatosplenomegaly. Organ complications characteristic of complicated malaria in non-immune adults have not been reported.

Pathophysiology and pathology of severe falciparum malaria

The essential pathological feature of severe falciparum malaria is sequestration of erythrocytes containing mature forms of the parasite in the deep vascular beds of vital organs. Sequestration is not uniformly distributed among the vital organs; in cerebral malaria it is usually greatest in the brain (MACPHERSON *et al.*, 1985; PONGPONRATN *et al.*, 1991), which may explain why cerebral malaria is such a prominent feature of severe falciparum malaria in humans, and least in the skin. Sequestration is also not uniformly distributed at a microvascular level.

Cerebral malaria and neurological abnormalities

Any pathophysiological explanation of the mechanism underlying cerebral malaria must take into account the clinical and pathological features of this condition. For example, the mortality of cerebral malaria ranges from 10% to 50% in treated patients, with an overall figure of 16% in children (WARRELL *et al.*, 1982; WHITE & HO, 1992; reviewed by WALLER *et al.*, 1995) yet, unlike almost all other febrile encephalopathies, most survivors have no easily detectable neurological deficit. Over 97% of adults, and approximately 90% of children, have no neurological abnormality on discharge from hospital (BREWSTER *et al.*, 1990). Unfortunately, despite considerable interest in immunopathological mechanisms in rodent models of severe malaria (GRAU *et al.*, 1989a; NEILL & HUNT, 1995) and also in the sequestering parasite *P. coatneyi* in rhesus monkeys (SEIN *et al.*, 1993b), there is no model which satisfactorily reproduces the clinical features of cerebral malaria in humans (WARRELL, 1987b; WHITE & HO, 1992). This has hampered progress in understanding pathophysiological mechanisms, and has led to several hypotheses of doubtful relevance to human disease.

The 'sludging' hypothesis

Early hypotheses were based on pathological observations of fatal cases of falciparum malaria; the cerebral capillaries were observed to contain a high proportion of parasitized cells, even when the peripheral parasitaemia was low (MARCHIAFAVA & BIGNAMI, 1894). Furthermore, the predominant forms in the cerebral capillaries and venules were large 'late' trophozoites and schizonts — forms seldom seen in peripheral blood films. It was suggested that these parasitized erythrocytes stuck together and had difficulty passing through the capillary bed. Flow was consequently reduced, and finally stopped (GASKELL & MILLAR, 1920). This was aptly termed 'sludging' (KNISELY *et al.*, 1941). The ensuing pathological events were considered to be the result of obstructed microcirculatory flow or the local release of unidentified toxic materials from the malaria parasites. Recent studies with fluorescein angiography have visualized the retinal capillary network in cerebral malaria *in vivo* and shown disruption consistent with microvascular occlusion (DAVIS *et al.*, 1992). The localized areas of retinal vessel whitening reported recently by LEWALLEN *et al.* (1998, 1999) may also represent localized areas of microvascular obstruction.

The permeability hypothesis

Cerebral oedema is a very common finding at autopsy in cerebral malaria (SPITZ, 1946; SEN GUPTA & NARAQI, 1992; WALKER *et al.*, 1992). Pathological observations in the 1940s (RIGDON, 1942) and animal studies in the 1960s led to a new hypothesis (MAEGRAITH & FLETCHER, 1972). The essential observations in these experiments were that in severely ill *P. knowlesi*-infected rhesus monkeys there was an increase in blood–brain barrier permeability to ^{125}I-labelled albumin and increased penetration of the brain by water-soluble dyes. The increased permeability was reversed rapidly by hydrocortisone, mepacrine, and chloroquine (MIGASENA & MAEGRAITH, 1967).

It was suggested that the primary pathophysiological abnormality in cerebral malaria was an increase in cerebral capillary permeability with outward leakage of plasma. This was considered to result in cerebral oedema and, because of the extravasation of plasma into the cerebral interstitium, local haemoconcentration and reduced microcirculatory blood flow. The factors responsible for this were considered to be kinins (MAEGRAITH & FLETCHER, 1972). This theory became widely adopted and was the basis for the widespread use of corticosteroids in cerebral malaria. Other agents to reduce the putative cerebral oedema were also recommended, such as urea and mannitol. Furthermore, it was suggested that some of the effects of quinoline antimalarial drugs such as chloroquine resulted from their anti-inflammatory activity. It has been suggested that chloroquine may be beneficial in severe malaria because of its anti-cytokine activity (KWIATKOWSKI & BATE, 1995), although there is no evidence of any benefit from chloroquine in patients who have received inappropriate treatment for severe chloroquine-resistant falciparum malaria.

The permeability hypothesis may be criticized on several grounds. Severe *P. knowlesi* infection in rhesus monkeys is clinically and pathologically unlike severe falciparum malaria in humans. Coma is not a prominent feature of the disease in monkeys and sequestration is not marked. Although a permeability defect was identified, the normal blood/cerebrospinal fluid albumin ratio was unchanged. This was not compatible with an increased influx of albumin from the blood, and so a novel and unfounded explanation was proposed: that of an increased bidirectional flux of albumin across the blood–brain barrier. This would have necessitated albumin transport out of the cerebrospinal fluid compartment against a 100:1 concentration gradient. There is now a series of clinical and experimental observations in adult humans which argue strongly against the permeability hypothesis. In the absence of spinal block, cerebral oedema leading to raised intracranial pressure must raise lumbar cerebrospinal fluid pressure. However, opening pressures at lumbar puncture are usually normal in 80% of adults. In children, opening pressures are similar to those recorded in adults but, because the normal range is considerably lower, 80% of these observations are above the normal range. Papilloedema is relatively unusual (LOOAREESUWAN *et al.*, 1983a; DAVIS *et al.*, 1992), although it may be more common in children than in adults (LEWALLEN *et al.*, 1993). Computed tomography of the brain rarely shows evidence of cerebral oedema (LOOAREESUWAN *et al.*, 1983b; NEWTON *et al.*, 1994). Magnetic resonance imaging is a more sensitive measure of brain water, but in a recent series from Thailand there was no evidence of cerebral oedema in 22 of 24 adult cases of cerebral malaria (LOOAREESUWAN *et al.*, 1995a). Chloroquine has no dramatic effect on level of consciousness in chloro-

quine-resistant falciparum malaria despite its undoubted anti-inflammatory activity. The clinical response to parenteral antimalarial chemotherapy is slow, yet reversal of the permeability defect in the monkey model is rapid. Two 'double-blind' placebo-controlled trials of medium and high dose dexamethasone in cerebral malaria showed no effect on mortality (WARRELL *et al.*, 1982; HOFFMAN *et al.*, 1988). In one of the trials, coma was prolonged in the steroid-treated patients (WARRELL *et al.*, 1982). Finally, in a series of studies of blood–cerebrospinal fluid barrier permeability in cerebral malaria, no consistent alteration in permeability was observed with a variety of marker substances which included ^{125}I-labelled albumin (BADIBANGA *et al*, 1986; WARRELL *et al.*, 1986). Recent immunohistopathological studies showed no evidence of protein leakage into the perivascular spaces of the brain in adult human cerebral malaria (G. Turner, personal communication). These observations indicate that cerebral oedema resulting from 'leaky' cerebral capillaries is not a consistent, or even a common, feature of cerebral malaria, and cannot, therefore, be the cause of coma in these patients. In fatal cases it is likely to be an agonal phenomenon.

Studies in adults with severe falciparum malaria, in which transcapillary escape rates for radio-labelled albumin and urinary micro-albumin excretion were measured and fluorescein angiography was used to demonstrate retinal capillary leakage, indicated a small but significant increase in generalized capillary permeability (DAVIS *et al.*, 1992). However, this was similar to that observed in patients with inflammatory conditions such as rheumatoid arthritis, and would be unlikely to account for any of the major pathological features of severe malaria. Thus there is no evidence for a severe and generalized increase in capillary permeability in severe falciparum malaria to the degree seen in other conditions such as the dengue shock syndrome.

It is likely that the post-mortem observation of cerebral oedema in fatal cases of cerebral malaria usually results from agonal events (hypotension, severe acidosis, etc.) which occur in the hours preceding death, but there is no clinical evidence that oedema precipitates death. A retrospective study of 25 fatal cases of falciparum malaria suggested that cerebral oedema was greater in 9 patients dying within 5 d of starting treatment than in 3 who survived for up to 14 d (HORSTMANN *et al.*, 1985). The authors considered that these results conflicted with the idea that cerebral oedema was a terminal phenomenon and they have been cited as evidence in favour of the permeability hypothesis (MAEGRAITH, 1989). However, it is difficult to interpret data from small numbers of patients who died after prolonged intensive care complicated by other infections, respiratory failure, renal failure treated by dialysis or haemoperfusion, hypoproteinaemia and serous effusion. In no case was cerebral sequestration of parasitized erythrocytes found at autopsy. This and other recent studies have been cited as evidence that cerebral malaria may occur in the absence of parasitized sequestration, but a much more prosaic explanation for these findings is that parasite clearance had occurred before death. There is no well-documented case of a patient dying untreated, or in the first 2 d following the beginning of antimalarial treatment, from cerebral malaria without the cerebromicrovasculature being packed with parasitized erythrocytes.

Recent autopsy studies of children dying of cerebral malaria in Malawi suggest important differences in pathophysiology compared to adults. In children, there is more evidence of an inflammatory response, with leucocytes and platelets in the cerebral microvasculature and increased permeability (T. E. Taylor, R. A. Carr & S. B. Lucas, personal communication).

The mechanical hypothesis

This hypothesis attempts to explain the pathophysiology of severe falciparum malaria by microcirculatory obstruction, with resulting local hypoxia and substrate depletion (i.e., ischaemia). Two principal mechanisms have been proposed to account for such obstruction, but in both cases the result is capillaries congested with red cells containing mature trophozoites and schizonts.

Decreased deformability. Normal erythrocytes must undergo considerable deformation in order to traverse the capillary and, when erythrocytes are unusually rigid, obstruction may occur. This is best illustrated in the crises of sickle cell disease.

It has been argued that erythrocytes containing mature parasites might be retained in capillaries by similar mechanisms. Studies in which individual cells were observed under different shear stresses have shown that erythrocytes infected with *P. falciparum* have reduced deformability, which is directly proportional to the maturity of the intracellular parasite (CRANSTON *et al.*, 1984). This explains the observation that such infected cells are less able to pass through micropore filters than uninfected cells (LEE *et al.*, 1982), which has also been demonstrated for the monkey malarias *P. knowlesi* (see MILLER, L. H. *et al.*, 1971) and *P. coatneyi* (see MILLER, L. H. *et al.*, 1972). Several factors are likely to account for reduced deformability of parasitized erythrocytes, notably changes in the cytoskeleton (MAGUIRE *et al.*, 1991), increased membrane stiffness, increased cytoplasmoic viscosity resulting from changes in membrane permeability (DUNN, 1969; KUTNER *et al.*, 1983), reduced surface area/volume ratio (increased sphericity) and, principally, the rigidity of the parasite itself (NASH *et al.*, 1989). The deformability of uninfected red blood cells is also reduced in severe malaria. In fatal cases red blood cell deformability is significantly lower than in survivors (DONDORP *et al.*, 1997).

There are theoretical objections to this rheological explanation of sequestration. If obstruction were due to cell rigidity, the site of the obstruction would be expected to be the site of minimum cross-sectional area, namely the mid-capillary. The 'tail' of erythrocytes stacked behind the obstructing cell should have a proportion of parasitized red cells similar to that of peripheral blood (WHITE, 1986). Furthermore, such obstruction should occur uniformly, as capillaries have similar internal diameters. This is in marked contrast to pathological observations showing (i) preferential sequestration in different vascular beds (MACPHERSON *et al.*, 1985; SEIN *et al.*, 1993a), (ii) that post-capillary venules are as important as the capillaries as sites for sequestration, and (iii) that affected capillaries are often packed solely with infected erythrocytes (MACPHERSON *et al.*, 1985). Finally, the rheological hypothesis cannot explain why *P. vivax*, which, in contrast to *P. falciparum*, enlarges the erythrocyte, does not also sequester.

Cytoadherence. Pathological studies show an intimate apposition of endothelial cell and infected erythrocyte membranes. This, and the inadequacy of the simple reduced red blood cell deformability hypothesis, led to the hypothesis that there was a specific molecular interaction causing infected erythrocytes to roll along, and then adhere to, the microvascular endothelium. The precise molecular mechanisms underlying this interaction have recently been characterized (see the review by BERNDT *et al.*, 1994). The post-capillary venule is the first site in a red blood cell's journey from the heart where the shear forces at the vessel wall drop markedly in a way which would permit such adherence. Infected red blood cells first roll, before finally sticking to the vascular endothelium. Uninfected erythrocytes will also bind to the surface of erythrocytes containing mature forms of the parasite, by a mechanism similar to that of cytoadherence to endothelial cells, causing 'rosetting'. This phenomenon is displayed *in vitro* by some parasite strains responsible for severe disease (CARLSON *et al.*, 1990; CARLSON, 1993). This may be important in the sequence of events leading to microvascular obstruction

but has not been demonstrated *in vivo* in humans (DAVID *et al.*, 1988; HANDUNNETTI *et al.*, 1989; UDOMSANGPETH *et al.*, 1989b). Using field isolates and laboratory-derived lines or clones, models of cytoadherence and rosetting have been developed *in vitro*. Such models have given information about both potential parasite adhesins and host receptors.

Parasite adhesins. Numerous stage-specific changes occur in the infected red blood cell membrane at the transition from non-sequestering ring form to the sequestering trophozoite (HOMMEL & SEMOFF, 1988). Electron-dense submembranous structures appear and enlarge, resulting in so-called 'knobs' which are visible by both scanning and transmission electron microscopy. These are the sites of adhesion between erythrocytes and endothelial cells and, although they are always seen in pathological studies of human malaria, they are not essential, as demonstrated by the description of knob-negative, cytoadhering parasite lines by 2 independent groups (BIGGS *et al.*, 1989; UDOPMSANGPETCH *et al.*, 1989a).

Knobs contain at least 2 histidine rich proteins (HRPs) which are parasite-derived and are exported to the erythrocyte membrane (HRP1 and HRP3). Since they are submembranous, they are not thought to participate directly in adhesion. They may perhaps serve to localize the cytoadherence ligand(s), making adhesion more effective.

Recently, there has been a breakthrough in the understanding of an important family of antigens exported by the parasite to the red blood cell surface. These proteins, known as *P. falciparum* erythrocyte membrane protein-1 (PfEMP-1) are large (200–350 kDa) molecules concentrated in the electron-dense knobs under the surface of parasitized erythrocytes (HOWARD, 1987, 1988). They show both clonal variation, allowing them to evade host immune responses, and adhesive properties involved in the cytoadherence phenomenon. During the search for drug resistance genes in *P. falciparum*, a family of more than 150 highly variable (*var*) genes was discovered, constituting about 6% of the whole *P. falciparum* genome. These *var* genes have been found to encode PfEMP-1. Several of the genes have now been sequenced, cloned and partially expressed, and binding of PfEMP-1 to several candidate endothelial receptors has been demonstrated (BARUCH *et al.*, 1995; SMITH, J. D. *et al.*, 1995; SU *et al.*, 1995). PfEMP-1 has also been implicated as the ligand for rosetting (CHEN *et al.*, 1998; FERNANDEZ *et al.*, 1998).

Cytoadherence can be inhibited by strain specific antisera (UDEINYA *et al.*, 1983; SINGH *et al.*, 1988). It has been proposed that PfEMP-1 may be the major surface antigen determining the population structure of *P. falciparum* (see GILBERT *et al.*, 1998); it has been shown to undergo antigenic variation at a rate of approximately 2·4% per parasite life cycle (ROBERTS, D. J. *et al.*, 1992).

Endothelial receptors. The stage and host cell specificity of cytoadherence suggests that the interaction between parasitized red blood cells and endothelial cells involves specific parasite ligands and host receptors. The search for these receptors has proved more difficult than originally expected and has relied heavily upon the use of models *in vitro*. *P. falciparum*-infected erythrocytes will adhere *in vitro* to a variety of cultured cell lines. When it was shown that they would adhere to cultured human umbilical vein endothelium, to monocytes and macrophages and to the amelanotic melanoma cell line C32 (UDEINYA *et al.*, 1981, 1983), it was assumed that the same receptor was being utilized on each cell type. This proved not to be the case, and at least 6 potential adhesins have been identified to date. The first to be discovered was CD36. The expression of CD36 on the surface of cells correlates with their ability to act as targets for cytoadherence of infected cells. This has been established with a panel of melanoma lines (PANTON *et al.*, 1987), by the induction of CD36 expression on U937 cells after phorbol ester stimulation (OCKENHOUSE & CHULAY, 1988), and by transfection of CDS7 cells with a complementary deoxyribonucleic acid (DNA) encoding CD36 (BERENDT *et al.*, 1989; OQUENDO *et al.*, 1989; M. Ho *et al.*, personal communication). Purified protein will inhibit binding in soluble form and will mediate binding if immobilized on plastic (OCKENHOUSE *et al.*, 1989). CD36 has been shown to bind directly to infected erythrocytes in the absence of thrombospondin and has been demonstrated on brain endothelium in patients both with and without cerebral malaria (BARNWELL *et al.*, 1989), although it is not thought to play a major role in cerebral sequestration. Recent studies have shown that nearly all freshly isolated parasites from patients with acute falciparum malaria bind strongly to CD36. Immunohistochemical studies indicate that parasite sequestration co-localizes with vascular expression of CD36 outside the brain, whereas within the brain there is very little CD36 expression and other ligands are presumably involved. This suggests that CD36 is probably the major cytoadherence ligand outside the brain.

The second candidate molecule to be discovered was thrombospondin, a multifunctional glycoprotein which is synthesized by many adherent cell types including endothelium and which is released on platelet activation (LAWLER, 1986). It plays a role in cell–cell and cell–matrix interactions. Purified thrombospondin will bind infected cells if it is immobilized on plastic (ROBERTS, D. D. *et al.*, 1985). Soluble thrombospondin or polyclonal antibodies will inhibit this interaction. Initial reports also suggested that cytoadherence to melanoma cells could be inhibited by these reagents, but other studies have found no inhibition with anti-thrombospondin antibodies (OCKENHOUSE *et al.*, 1989; OQUENDO *et al.*, 1989; SHERWOOD *et al.*, 1989). Furthermore, not all melanoma cell lines secreting thrombospondin mediate cydoadherence.

These data suggest that, while thrombospondin may contribute to cytoadherence, possibly by stabilizing the PfEMP-1–CD36 interaction, it alone does not mediate it.

Studies on field isolates of malaria parasites in The Gambia showed no correlation between the ability of infected cells to bind to C32 melanomas and the severity of disease, notably cerebral malaria (MARSH *et al.*, 1988). This implied that yet other receptors might exist, particularly on cerebral endothelium. Studies with COS cell transfectants and human umbilical vein endothelium have identified intercellular adhesion molecule 1 (ICAM-1) as a cytoadherence receptor for *P. falciparum* (see BERENDT *et al.*, 1989). This is also the natural receptor for rhinovirus invasion, although the binding sites for malaria parasites and the rhinovirus are different. Although most natural isolates bind less avidly to ICAM-1 than to CD36 (OCKENHOUSE *et al.*, 1991), recent immunohistochemical studies indicate highly significant co-localization of parasite sequestration within the brain and vascular expression of ICAM-1. This suggests that ICAM-1 is probably the major vascular ligand for cytoadherence within the brain (TURNER *et al.*, 1994). The interaction between ICAM-1 and infected red blood cells is of a 'rolling' type, in which the cell rolls along the vascular endothelium somewhat analogously to the movement of a polymorphonuclear leucocyte before it penetrates at a site of inflammation (NASH *et al.*, 1992). This contrasts with the static adhesion resulting from binding to CD36. Flow-based assays may be a more realistic and therefore useful model of cytoadherence *in vivo* than static assays (COOKE *et al.*, 1996).

Recently, 4 other potential ligands have been identified; E-selectin (ELAM-1), V-CAM-1, chondroitin sulphate, and PECAM-1/CD31 (TREUTIGER *et al.*, 1997). Their role is less clear. The glucose aminoglycan, chondroitin sulphate A (CS-A) (ROGERSON *et al.*, 1995), is

expressed on placental vascular endothelium. Recent studies suggest that parasites which sequester in the placenta are a CS-A binding subset (FRIED & DUFFY, 1996). The increased susceptibility of primigravidae to falciparum malaria-associated low birth weight may be explained by a relative lack of antibodies which compete with CS-A binding (FRIED *et al.*, 1998).

Some of these ligands, such as CD36 and thrombospondin, seem to be expressed at all times in a wide range of vascular beds and are able to bind *in vitro* to all 'wild' isolates of *P. falciparum*. They are regarded as constitutive and their expression is not related qualitatively or quantitatively to disease severity. Other receptors, such as ICAM-1 and ELAM-1, are inducible (show increased expression or are expressed only) in the cerebral blood vessels of patients with cerebral malaria, suggesting that they may be responsible for cytoadherence in this disease (BERENDT *et al.*, 1989; TURNER *et al.*, 1994). TNFα and other inflammatory mediators are able to induce this expression.

Obstruction of the cerebral microvasculture, as envisaged by the mechanical hypothesis, should result in a global reduction of cerebral blood flow in cerebral hypoxia. In adult patients with cerebral malaria in Thailand there was no absolute reduction in cerebral blood flow (WARRELL *et al.*, 1988). However, cerebral blood flow was low in relation to arterial oxygen content, one of its major determinants. Cerebral oxygen consumption and cerebral arteriovenous oxygen content difference were decreased and cerebral venous pO_2 was increased. There was no significant change in cerebral blood flow, cerebrovascular resistance, or cerebral metabolic rate when comatose patients became rousable. However, arterial lactate concentration and cerebral lactate production were significantly higher when the patients were in coma. Cerebrospinal fluid concentrations of lactate were elevated in all but one of 45 patients with acute cerebral malaria, and were significantly higher in fatal cases than in survivors (WHITE *et al.*, 1985, 1987a; PE-THAN-MYINT *et al.*, 1987; TAYLOR *et al.*, 1988).

It is not possible to extrapolate from peripheral arterial and venous substrate and metabolite concentrations to events within the cerebral capillaries because there may be local substrate (e.g., glucose) depletion and metabolite (e.g., lactate) accumulation in areas of low flow which are not reflected in the peripheral blood.

These studies suggest that there is anaerobic cerebral glycolysis in cerebral malaria, which presumably results from cerebral hypoxia. There is also a significant contribution from the parasites' glycolytic metabolism (JENSEN *et al.*, 1983). Cerebral hypoxia may well result from either 'patchy' microcirculatory obstruction with adjacent areas of increased perfusion or, alternatively, a more diffuse and homogeneous process in which the adherent erythrocytes interfere with gas and substrate exchange throughout the brain but do not increase vascular resistance. The most likely scenario is vasodilation to accommodate the increased intracerebral blood volume (sequestered plus circulating erythrocytes) (LOOAREESUWAN *et al.*, 1995a).

The immunological hypothesis

Immune mechanisms appear to be important in the pathogenesis of certain severe manifestations of malaria in rodents such as glomerulonephritis in rats (EHRICH *et al.*, 1984), and cerebral lesions in certain strains of mice (REST, 1982; GRAU, 1989a; SCHETTERS *et al.*, 1989). Immune mechanisms have not been proved to have a role in the pathogenesis of cerebral malaria. Malaria infections induce both cellular and humoral immune responses, and there is evidence of complement activation in acute malaria in humans (ADAM *et al.*, 1981). The neuropathological findings in cerebral malaria have been interpreted as resulting from a 'hyperergic' reaction of the central nervous system to the antigenic challenge of *P. falciparum* infection (TORO & ROMAN, 1978), but the predicted increase in brain water content associated with this (ROMAN & SENANAYAKE, 1992) was not observed by magnetic resonance imaging *in vivo* (LOOAREESUWAN *et al.*, 1995a). The proposed mechanism for this was an immune complex vasculitis of the cerebral vessels. However, the perivenous demyelination described by these authors could have been explained by terminal hypoxia. Furthermore, histopathological studies, immunohistochemical studies, and ultrastructural studies usually show no evidence of an inflammatory cell infiltrate despite abundant evidence of endothelial cell activation (MACPHERSON *et al.*, 1985; TURNER *et al.*, 1994). Proponents of the 'immunological' hypothesis have often cited pathological studies in which patients died with little or no cerebral sequestration — but these referred to late deaths well after parasite clearance and may not be informative concerning acute pathological processes. Proliferative glomerulonephritis, the classical pathological marker of an immunological disease, has also been reported in falciparum malaria (HARTENBLOWER *et al.*, 1972). However, histological evidence of vasculitis is absent from fatal cases of falciparum malaria. Although immune complexes and free malarial antigen may be detected in the glomerulus and there may be an increase in cellularity, clinically significant glomerulonephritis is exceedingly rare; acute tubular necrosis is the usual lesion (STONE *et al.*, 1972). A model of cerebral malaria in CBA/Ca mice has been described by P.-H. Lambert and his colleagues (GRAU *et al.*, 1986, 1987a). However, both the clinical features and histopathological appearances are quite different from those in human cerebral malaria. A subparasiticidal dose of cyclosporin A reduced mortality in this model, suggesting an immunological mechanism. However, cyclosporin A had no effect on the mortality of human cerebral malaria in a 'double-blind' placebo-controlled trial carried out in Ho Chi Minh City (Trinh-Kim-Anh, personal communication). PATNAIK *et al.* (1994) have recently reported that mononuclear cell margination along the cerebral microvascular walls was prominent in 5 of 23 fatal cases of cerebral malaria, and speculated that this may have contributed to pathology. Although the immunopathological findings in one fatal case of cerebral malaria reported from Switzerland were reported to be similar to those observed in murine models, this patient was an intravenous drug addict with acquired immune deficiency syndrome (AIDS), and this may have complicated the pathological findings (PORTA *et al.*, 1993).

The hypocomplementaemia of falciparum malaria is not associated with any specific pattern of target organ damage. It appears simply to reflect the severity of infection (P. Malasit, personal communication). Infusions of antibody in owl monkeys (*Aotus* sp.) with *P. falciparum* infection were beneficial in this primate model (DAVID *et al.*, 1983), but were of no clinical benefit in human cerebral malaria (KWIATKOWSKI *et al.*, 1993). Blood transfusion from hyperimmune donors is not associated with untoward reactions. Corticosteroids are harmful in cerebral malaria (WARRELL *et al.*, 1982).

Thus, although immune mechanisms may well be important in delayed cerebellar ataxia and in chronic processes such as quartan nephropathy and tropical splenomegaly, the evidence for their involvement in the pathogenesis of acute cerebral malaria remains unconvincing.

Cytokines

The concept that severe malaria may be mediated by the products of activated macrophages derives from observations on the similarity between severe malaria and endotoxaemia (CLARK *et al.*, 1981). In recent years a considerable body of evidence has emerged to support the concept that cytokines, and in particular TNF, may play an important role in causing some of the patholog-

ical changes that characterize malaria. Much of this evidence originally derived from studies in rodent models of severe malaria (GRAU *et al.*, 1986). In murine models, immunopathological damage results in the presence of activated CD4+ T cells, is associated with elevated concentrations of TNF, and can be prevented by the administration of anti-TNF polyclonal antibodies (GRAU *et al.*, 1987b, 1987c). This treatment does not influence parasitaemia and, although it protects from cerebral damage, the mice ultimately die of anaemia. Detailed studies have shown that CD4+ cell activation leads to the production of pro-inflammatory cytokines which up-regulate a variety of macrophage functions, one of which is the release of TNF. Elevated concentrations of TNF and other cytokines alter the surface properties of vascular endothelial cells and result in the local accumulation of leucocytes. These sequestered leucocytes release more TNF, thus amplifying the cytotoxic effect on endothelial cells, and resulting ultimately in vascular wall damage and haemorrhagic necrosis. In this murine model, sequestration of leucocytes and monocytes is the predominant pathological finding. In this respect it differs fundamentally from severe falciparum malaria in humans. The apparent adverse effect of pro-inflammatory cytokines on the host are balanced by evidence of an anti-parasitic effect. These cytokines synergize with other host defence mechanisms to limit parasite multiplication. The anti-parasitic effect is not a direct effect of cytokines, as these are not directly cytotoxic to intraerythrocytic parasites *in vitro* (TAVERNE *et al.*, 1987; CURFS *et al.*, 1990). One of the main toxic serum components appears to be lipid peroxides (ROCKETT *et al.*, 1988), which are formed by the interaction of lipoproteins with reactive oxygen intermediates. Malaria parasites are extremely susceptible to free radical damage (MALHOTRA *et al.*, 1988) and lipid peroxidation has the effect of stabilizing the reactive oxygen groups, thus creating a more stable cytotoxic molecule.

Induction of cytokine release. Soluble antigens of *P. falciparum* released *in vitro* into culture supernatants, and also found in the plasma of patients with acute malaria, are potent inducers of TNF release from monocytes and macrophages (BATE *et al.*, 1990; KWIATKOWSKI *et al.*, 1989; TAVERNE et al., 1990a, 1990b). These antigens share many of the properties of bacterial lipopolysaccharides in that they react in the limulus lysate assay (and probably explain the positivity of this assay in severe malaria) (USAWATTANAKUL *et al.*, 1985). However, the ability of *P. falciparum* to induce pro-inflammatory cytokine release is considerably lower than that of Gram-negative bacteria. For example, patients with one or more colony-forming units/mL of Gram-negative bacteria have a 20% mortality rate, whereas comparable mortality is not reached with blood concentrations of malaria parasites over 100 000 000 times higher than this (WHITE, 1998). The *P. falciparum*-derived cytokine-inducing exoantigens in rodents induce a T cell independent antibody that blocks their ability to induce TNF release. Although these antigens share many characteristics with lipopolysaccharides, there are also differences. Inhibition by polymixin B is variable, and certain strains of mice (C3H/HeJ) which are hyporesponsive to lipopolysaccharides secrete TNF normally in response to these antigens (TAVERNE *et al.*, 1990b), which suggests a different macrophage receptor interaction (reviewed by KWIATKOWSKI, 1995). Synchronous release of these exoantigens at schizont rupture is thought to mediate fever. The precise molecular structure of the malaria pyrogen has not yet been characterized. It has been associated with malaria pigment (PICHYANGKUL *et al.*, 1994), but whether this is a good absorptive surface and presentation vehicle for the putative toxin, or whether the pigment itself is the mediator, has not been resolved. Cytokine release is induced without a requirement for accompanying T cell activation. There is increasing evidence that premunition represents 'tolerance' to these lipopolysaccharide-like substances. Thus, with repeated exposure, successive infections induce progressively less cytokine release (BATE *et al.*, 1990; PLAYFAIR *et al.*, 1990). This would explain why anti-disease immunity develops more rapidly than strain-specific immunity.

Human studies. Several studies now have confirmed a positive association between plasma concentrations of TNF and other pro-inflammatory cytokines, and mortality in severe falciparum malaria (GRAU *et al.*, 1989b; KERN, P. *et al.*, 1989; KWIATKOWSKI *et al.*, 1990; KRISHNA *et al.*, 1994a), although some studies have failed to confirm such a relationship (SHAFFER *et al.*, 1991). In most of these studies plasma concentrations of TNF have been correlated with several indicators of severity, namely hypoglycaemia, hyperparasitaemia, and anaemia. Plasma concentrations of interleukin (IL) 1 (KWIATKOWSKI *et al.*, 1990), IL-6 (KERN, P. *et al.*, 1989), and IL-8 (FRIEDLAND *et al.*, 1993) have also been shown to be correlated with disease severity. IL-10 inhibits the ability of malaria antigens to induce or release tumour necrosis factor (HO *et al.*, 1995), and recent studies suggest that in severe malaria, particularly in fatal cases, there is a relative failure of IL-10 production, and thus of control of pro-inflammatory cytokine release (HO *et al.*, 1998; N. P. J. Day and M. Ho, personal communication). In recent studies in The Gambia, a genetic polymorphism in the TNF promoter region has been shown to confer a seven-fold increased risk of either death or neurological deficit from severe malaria (MCGUIRE *et al.*, 1994). If this promotor polymorphism is shown to be associated with augmented TNF production, this would strongly suggest a link between TNF production and potentially lethal events, but there are several problems with the cytokine story. First, there is considerable overlap in the range of cytokine levels that have been recorded in different patient groups with malaria. Plasma concentrations of pro-inflammatory cytokines are very high in *P. vivax* malaria, particularly following schizogony in synchronous infections (KARUNAWEERA *et al.*, 1992), but *P. vivax* is not lethal. Second, there are differences between the clinical manifestations of severe malaria and lethal septic shock — a condition in which there is good evidence for cytokine-mediated pathology (DANNER *et al.*, 1991). Third, the animal models in which a role for direct cytokine induced pathology is strong are pathologically distinct from fatal severe malaria. Early studies used non-specific assays which measured both free biologically active TNF and also TNF bound to circulating receptors. Free TNF has a very brief circulatory half-life (5–20 min) (MICHIE *et al.*, 1988), and most TNF measured represents biologically inert mediator bound to circulating receptors. Increased concentrations of TNF receptors, particularly R75, are found in severe malaria (KERN, P. *et al.*, 1992; KERN, W. V. *et al.*, 1993). The relationship between TNF production and its neutralization by tissue-bound and circulating receptors is an important determinant of the biological effects. If pro-inflammatory cytokines do play a central role in severe malaria, these pathological events are likely to take place locally and may not be reflected in systemic cytokine measurements. Some of these uncertainties should be resolved by studies of anti-TNF antibodies in severe malaria. Preliminary studies indicate that these are antipyretic, confirming a central role for TNF in fever induction (KWIATKOWSKI *et al.*, 1993). Studies to date indicate that anti-TNF antibodies are antipyretic, but there was no evidence of clinical benefit — indeed there was a slight increase in neurological sequelae in recipients of anti-TNF antibodies (KWIATKOWSKI *et al.*, 1993; VAN HENSBROEK *et al.*, 1997).

The cause of coma

Many hypotheses have been proposed to explain loss of consciousness in severe malaria. None is completely

satisfactory. Ischaemia alone would not account for the excellent neurological recovery. Similar cerebral metabolic findings to those in cerebral malaria have been reported in volunteers breathing low concentrations of oxygen (reviewed by WHITE & HO, 1992). Inflammatory processes are not compatible with the time course or pathology. Increased systemic levels of pro-inflammatory cytokines may obtund but do not lead to profound coma.

Cerebral malaria resembles a metabolic or anaesthetic encephalopathy (WHITE & HO, 1992). Abnormalities of neurotransmitter synthesis, release or binding may eventually be implicated (CLARK & ROCKETT, 1996). Recently, it has been suggested that the ubiquitous messenger nitric oxide may be implicated. However, it is also worth considering that coma may be neuroprotective. Neurones stressed by an inadequate supply of oxygen and nutrients, and an unfavourable metabolic milieu, may preserve themselves by reducing energy demands. Premature reversal of coma might increase the risk of neuronal damage.

Raised intracranial pressure in cerebral malaria

Raised intracranial pressure is thought to play an important role in the pathogenesis of many encephalopathic processes (MINNS, 1991). There have been sporadic reports suggesting that raised intracranial pressure may be a feature of cerebral malaria (BERGERET, 1948; ROTHE, 1956; GELFAND, 1973; SCHMUTZHARD & GERSTENBRAND, 1984; THAPA *et al.*, 1988) and even that osmotherapy might have a role in its management (KINGSTON, 1971; COMMEY *et al.*, 1980), but this has not been subjected to controlled trial. However, in carefully conducted studies the opening pressure at lumbar puncture was normal in the majority of non-immune adults with cerebral malaria, and lower in those who died (WARRELL *et al.*, 1986). This, taken together with evidence that cerebral oedema in adults with cerebral malaria is probably an agonal event (LOOARESUWAN *et al.*, 1983b) and that dexamethasone has a deleterious effect (WARRELL *et al.*, 1982), suggested that raised intracranial pressure, at least in non-immune adults, did not play an important role in the pathogenesis of cerebral malaria. However, recent studies of intracranial pressure in African children with cerebral malaria have forced a reappraisal of this view. NEWTON *et al.* (1991), in a study of 26 Kenyan children, found that cerebrospinal fluid opening pressure at lumbar puncture was raised in all cases. These observations have been confirmed in studies of children in The Gambia (WALLER *et al.*, 1991) and Malawi (LEWALLEN *et al.*, 1993). Subsequent studies in Kenya, employing direct intracranial pressure monitoring, have provided a more detailed picture of the development and possible role of intracranial hypertension (NEWTON *et al.*, 1997b). Twenty-three children with strictly defined cerebral malaria were monitored. Children whose coma was due to a prolonged post-ictal episode or who were severely acidotic were excluded. All the children had raised intracranial pressure, and in 10 this was considered mild, cerebral perfusion pressure was maintained above 50 mm Hg, and there was no rise in intracranial pressure above 20 mm Hg for more than 15 min. Thirteen children had intracranial hypertension of a degree which would normally merit specific intervention. In 9 cases this was moderately severe, with intracranial pressures between 20 and 40 mm Hg and cerebral perfusion pressure falling below 50 mm Hg for periods of more than 15 min, but not below 40 mm Hg. Four children had severe intracranial hypertension with intracranial pressure above 40 mm Hg and cerebral perfusion pressure below 40 mm Hg for more than 15 min.

Pathogenesis of raised intracranial pressure. A rise in intracranial pressure may damage the brain by 2 main mechanisms: (i) brain tissue may herniate downwards, causing compression of vital structures (coning); (ii) cerebral blood flow may be compromised. Cerebral blood flow depends mainly on cerebral perfusion pressure (the difference between the mean arterial pressure of blood entering the intracranial space and intracranial pressure). Under normal circumstances central blood flow is maintained by a series of protective responses. Initially, cerebral perfusion pressure itself is maintained by compensatory rises in mean arterial pressure in the face of a rising intracranial pressure (the Cushing response). Even if cerebral perfusion pressure does rise, central blood flow is further protected by a series of autoregulatory responses (MINNS, 1991). None the less, there is a limit to compensatory mechanisms and if this is exceeded cerebral blood flow is compromised. This may be exacerbated if other pathogenic processes interfere with normal components of autoregulation.

Intracranial pressure rises if there is an increase in intracranial cerebrospinal fluid, blood or brain volume. There is no evidence of acute hydrocephalus in cerebral malaria in either adults (LOOARESUWAN *et al.*, 1983b) or children (NEWTON *et al.*, 1994). CT studies (LOOARESUWAN *et al.*, 1983b) in immune adults indicated that cerebral oedema was rare and an agonal event. Six of 14 Kenyan children with cerebral malaria had evidence of diffuse brain swelling on CT scans performed between 3 d and 9 d after the onset of symptoms (NEWTON *et al.*, 1994). In 2 cases this resolved completely and these children made complete recoveries. In the other 4 children, diffuse brain swelling was associated with hypodense lesions and loss of grey–white matter differentiation. These appearances are compatible with cytotoxic oedema secondary to cellular damage. All 4 children had prolonged coma and severe sequelae, and 2 who had intracranial pressure monitored had severe intracranial hypertension.

The CT data, taken together with information on the natural history of raised intracranial pressure (NEWTON *et al.*, 1996), suggested that, in the majority of children who have mild or moderate raised intracranial pressure, the most likely scenario is a short episode of brain swelling which is likely to be due to an increase in cerebral blood volume. The basis of increased cerebral blood volume remains speculative but several key processes may interact. Thus sequestration of infected red blood cells may act as the equivalent of a diffuse intracranial mass and further contribute to an increase in volume by impeding venous drainage. Both acidosis and nitric oxide production are potent vasodilators. Anaemia may contribute to increased cerebral blood flow by lowering viscosity in addition to its role in the genesis of lactic acidosis. Finally, seizures lead to an increase in central blood flow and lead to acute rises in intracranial pressure. In the minority who develop severely raised intracranial pressure, this is associated with cytotoxic oedema secondary to cellular damage.

Signs of intracranial hypertension. No combination of clinical or laboratory signs was useful in identifying children who subsequently developed dangerous levels of intracranial hypertension (NEWTON *et al.*, 1996). Initial intracranial pressure at the beginning of monitoring (equivalent to opening pressure at lumbar puncture) was not related to maximum intracranial pressure or minimum cerebral perfusion pressure. Children in deepest coma on admission tended to develop higher intracranial pressures but this was not useful on an individual basis. Decerebrate motor responses, pupillary dilatation, decerebrate posturing, or absent oculocephalic responses were not related to the subsequent development of moderate or severe intracranial hypertension. Absent or sluggish pupillary responses were predictive but were not observed in the majority of children developing significant intracranial hypertension. Papilloedema was present in only one child on admission (with severe intracranial hypertension) and developed during monitoring in a second after the development of severe intracranial hypertension. Fun-

dal haemorrhages were common but not associated with the degree of raised intracranial pressure. Seizures were common but did not reflect the degree of intracranial hypertension. They did, however, cause significant rises in intracranial pressure during the episode and for several minutes afterwards.

Relationship of raised intracranial pressure to outcome. In the original series of observations on Kenyan children (NEWTON *et al.*, 1991), clinical signs consistent with rostrocaudal progression of brain stem herniation occurred in 9 of 12 children (75%) who died, leading to the suggestion that herniation as a result of raised intracranial pressure was the mode of death in some children with cerebral malaria. Intracranial pressure monitoring and Doppler ultrasonography studies do suggest significant intracranial hypertension in some children who have clinical signs of uncal and mid-brain herniation (NEWTON *et al.*, 1996, 1997b). However, this observation must be tempered by recognition that these clinical signs attributed to herniation are observed commonly in survivors of severe childhood malaria and therefore cannot be specific for lethal herniation syndromes. Furthermore, the autopsy evidence to date, both in children and adults with severe malaria, suggests that either uncal or foramen magnum herniation is rare as a cause of death.

However, it seems certain that raised intracranial pressure does play a role in the terminal events in some cases and, in the one child who died during the course of direct intracranial pressure monitoring, intracranial pressure rose to critical levels as the child developed signs of uncal and mid-brain herniation (NEWTON *et al.*, 1996). This is further supported by the observation that 3 of 6 children monitored by transcranial Doppler ultrasonography had findings strongly suggestive of progressive intracranial hypertension associated with clinical signs of herniation terminating in death (NEWTON *et al.*, 1996).

The mean spinal tap opening pressure at the time of admission to hospital is similar in children with cerebral malaria who survive and in those who die (KWIATKOWSKI *et al.*, 1991; WALLER *et al.*, 1995). This observation does not exclude a role for raised intracanial pressure in contributing to death in some patients, since intracranial pressure fluctuates over time and is poorly reflected in a single measurement of opening pressure.

There is no evidence from the pattern of abnormalities seen on CT scans either acutely (NEWTON *et al.*, 1994) or at follow-up (N. Peshu, personal communication) that herniation plays a role in the development of neurological sequelae following cerebral malaria. Studies in children in whom intracranial pressure was monitored continuously have not resolved the role of raised intracranial pressure in the pathogenesis of neurological sequelae (NEWTON *et al.*, 1996). The situation in cerebral malaria is complicated by the presence of other pathogenic processes likely to cause neurological sequelae, notably status epilepticus and hypoglycaemia. Thus, reduced cerebral perfusion pressure secondary to raised intracranial pressure could play a role in the development of neurological sequelae, but its effects, and the level at which it is important, are likely to vary depending on the presence of other pathogenic processes.

Anaemia

Anaemia is an inevitable consequence of malaria infection, especially in children (MCGREGOR *et al.*, 1956; HENDRICKSE & KING, 1958). Anaemia develops rapidly in the course of severe malaria and, in general, the more severe the infection the faster and greater the drop in haematocrit. In children, and occasionally in pregnant women, severe malaria may present as profound anaemia combined with a high parasite count (>100 000/μL). In areas of high stable transmission, the presentation of severe anaemia is the most important manifestation of severe malaria and occurs predominantly in children less than 3 years of age. A haematocrit <13% (haemoglobin <4 g/dL) is associated with a significant increase in mortality in children presenting with malaria. The rate at which anaemia develops is obviously an important determinant of compensatory mechanisms such as the rightward shift in the oxygen dissociation curve. Hyperventilation (often termed respiratory distress) is an important indicator of decompensation.

The mechanisms of anaemia are multifactorial and complex, involving haemolysis and an inappropriate bone marrow response (SRICHAIKUL *et al.*, 1967; WEATHERALL & ABDALLA, 1982). There is initial iron sequestration with low serum iron level, but massive hyperferritinaemia. Dyserythropoietic changes in the bone marrow of patients with malaria have been described by KNÜTTGEN (1963), ABDALLA *et al.* (1980), PHILLIPS *et al.* (1986a) and WICKRAMASINGHE *et al.* (1987). Dyserythropoietic changes have also been found in the marrow of patients with vivax malaria, most of whom did not become anaemic (WICKRAMASINGHE *et al.*, 1989). Cytokines, notably TNF, are known to depress erythropoiesis (SASSA *et al.*, 1983) and contribute to dyserythropoiesis and phagocytosis in murine models of malaria (CLARKE & CHAUDHRI, 1988). The electron microscopical study carried out by WICKRAMASINGHE *et al.* (1987) in Thai patients with cerebral malaria showed that a high percentage of the red blood cells within marrow sinusoids were parasitized and that these cells were attached to the endothelium. Some marrow sinusoids were packed, or even completely obstructed, by parasitized cells. The appearance of reticulocytes in the peripheral blood is delayed, but the marrow appears active throughout, with normal myeloid/erythroid ratios (PHILLIPS *et al.*, 1986a).

Immune-mediated haemolysis has been suggested as the mechanism of anaemia among children in the holoendemic area of West Africa. There was evidence that red blood cells were sensitized with C3 complement (FACER *et al.*, 1979; FACER, 1980). However, in the same area, ABDALLA (1986) found no increase in the number of immunoglobulin (Ig) G molecules bound to red blood cells in patients with malaria compared to that in controls. There was no correlation between severity of anaemia and red blood cell-associated IgG levels. Similarly, in Thailand, patients with falciparum malaria showed no increase in IgG coating of their red blood cells and there was no correlation between the severity of anaemia and these levels (MERRY *et al.*, 1986). However, a strong correlation was found between anaemia and the clearance of erythrocytes coated with relatively low numbers of IgG molecules (HO *et al.*, 1990). LOOAREESUWAN *et al.* (1987b), also in Thailand, demonstrated increased rates of erythrocyte destruction following clearance of *P. falciparum* and *P. vivax* parasitaemias. Red blood cell clearance rates were increased in proportion to disease severity and were highest in patients with severe malaria (LOOAREESUWAN *et al.*, 1991). This enhanced clearance was more marked with compatible donor erythrocytes than with autologous cells and was not mediated by antibody or complement. These observations suggested an exoerythrocytic factor such as non-specific activation of the reticuloendothelial system. Patients with splenomegaly showed markedly accelerated clearance of labelled heat-damaged erythrocytes and a lower mean haematocrit than those without splenomegaly (LOOAREESUWAN *et al.*, 1987a). In the patients without splenomegaly, clearance of heat-damaged cells rapidly increased after the start of antimalarial chemotherapy. Enhanced clearance persisted for several weeks but was normal after 6 weeks in both groups of patients. Red blood cells coated with IgG are more rapidly removed from the circulation by the spleen in patients convalescing from malaria than in healthy controls (LEE *et al.*, 1989). All these data indicate that the spleen is a major

site of erythrocyte destruction in malaria and that its threshold for recognizing cells to be removed from the circulation is lower than normal, both for mechanical filtration and Fc receptor-mediated removal.

Haemoglobinuria and blackwater fever

Sensitization of red blood cells to quinine, after the intermittent use of this drug as a prophylactic, was thought by most authorities to be the cause of blackwater fever, an idea that was supported by some laboratory studies and the virtual disappearance of the condition when quinine was replaced by synthetic antimalarial drugs (MUIRHEAD *et al.*, 1958; ADNER *et al.*, 1968; CANFIELD, 1969). Classical blackwater fever may now be extinct, but haemoglobinuria may occur in overwhelming infections and in patients with red blood cell abnormalities. Studies of haemoglobinuria in Viet Nam have shown that blackwater fever occurs in 3 circumstances: (i) in patients with G-6PD deficiency who take oxidant drugs or foodstuffs; (ii) in patients with G-6PD deficiency who have acute malaria and receive antimalarial treatment with quinine or an artemisinin derivative; and (iii) in patients with acute, often severe, malaria who have normal red cell G-6PD concentrations.

The cause of haemolysis in this group (iii) is unknown. Patients with blackwater fever often have multiple episodes associated with febrile illnesses (not necessarily malaria). Only a minority of patients with black urine will develop renal impairment, although this remains an important cause of renal failure. The cause of renal failure in patients with malarial haemoglobinuria is uncertain. Large doses of quinine used as an abortifacient have caused fatal renal tubular necrosis attributed to haemoglobinuria (TERPLAN & JAVERT, 1948; LANG & JONES, 1964). Haemoglobin itself is not nephrotoxic in well-hydrated animals and humans (BRANDT *et al.*, 1951; CONN *et al.*, 1956; NG & SUKI, 1980) and many patients with haemoglobinuria do not develop renal failure, but other compounds released from lysed erythrocytes can induce acute tubular necrosis, especially in the presence of dehydration and acidosis (HAMILTON-FAIRLEY & BROMFIELD, 1934; BLACKBURN *et al.*, 1954; DE MARIA & HARRIS, 1955; JAENIKE, 1967; SCHMIDT HOLLAND, 1967).

Jaundice

Hyperbilirubinaemia is attributable to intravascular haemolysis of parasitized erythrocytes, hepatic dysfunction, and possibly an element of microangiopathic haemolysis associated with disseminated intravascular coagulation.

Impairment of hepatic function is common in severe malaria (WARRELL & FRANCIS, 1999). Unfortunately, assessment of 'liver function' by measurement of blood concentrations of bilirubin and liver-related enzymes is notoriously imprecise, particularly in the presence of coexisting haemolysis. Jaundice is more common in adults with severe malaria than in children (WHITE & HO, 1992; WALLER *et al.*, 1995). The measurable consequences of hepatic dysfunction are coagulation abnormalities resulting from failure to synthesize clotting factors (which may be complicated by the consumption of clotting factors), hypoalbuminaemia, and reduced metabolic clearance of many substances including alanine and lactate (often associated with hypoglycaemia) (WHITE *et al.*, 1983a, 1987a; TAYLOR *et al.*, 1988), and antimalarial drugs (TRENHOLME *et al.*, 1976; WHITE, 1985). Biotransformation of drugs, particularly those metabolized by hepatic microsomal enzymes, is reduced in proportion to disease severity. Hepatic blood flow, measured by indocyanine green (ICG) clearance, is reduced during acute malaria, and is significantly lower in severe malaria than in uncomplicated malaria; it returns to normal during convalescence (MOLYNEUX *et al.*, 1989a; PUKRITTAYAKAMEE *et al.*, 1992, 1994). ICG clearance may reflect not only liver blood flow but also biliary excretion. Galactose clearance, an alternative measure of liver blood flow, and also glycerol clearance have been found to be relatively unperturbed by malaria (PUKRITTAYAKAMEE *et al.*, 1992, 1994). These data suggest that sequestration and consequent microcirculatory obstruction in the portal and hepatic circulations, or portal venoconstriction as demonstrated in rhesus monkeys infected with *P. knowlesi* (see SKIRROW *et al.*, 1964), is unlikely to be the sole cause of liver dysfunction. Clearly some metabolic processes, such as gluconeogenesis, are more perturbed than others. ICG estimates of liver blood flow are closely related to hyperlactataemia: flows <15 mL/kg/min are associated with a progressive rise in plasma lactate concentrations (PUKRITTAYAKAMEE *et al.*, 1994).

Jaundiced patients may be diagnosed as having 'malaria hepatitis' (DELLER *et al.*, 1967). Liver biopsy usually reveals Kupffer cell hyperplasia and mononuclear cell infiltration. In addition, pigment deposits are prominent (SRICHAIKUL, 1959). Other studies have shown either no structural change or slight hepatocyte swelling (SHERLOCK, 1975). Centrizonal necrosis has been reported (RIGDON & STRATMAN-THOMAS, 1942; JOSHI *et al.*, 1986). Measurement of the metabolic clearance of probe drugs provides a more sensitive measure of liver function. Acute malaria adversely affects the function of a broad array of cytochrome P450 microsomal enzymes, and also impairs conjugation reactions (PUKRITTAYAKAMEE *et al.*, 1997).

Haemostatic abnormalities, thrombocytopenia

Activation of the coagulation cascade occurs even in mild malaria, but the degree of activation is proportional to disease severity (PUKRITTAYAKAMEE *et al.*, 1989). The activation of the coagulation cascade in malaria is through the intrinsic pathway (CLEMENS *et al.*, 1994).

The role of disseminated intravascular coagulation in severe falciparum malaria has probably been overemphasized. UDEINYA & MILLER (1987) demonstrated *in vitro* a procoagulant effect of *P. falciparum*-infected erythrocytes on platelet-poor human plasma in the presence of Russell's viper venom. Accelerated fibrinogen catabolism (DEVAKUL *et al.*, 1966) and elevated blood concentrations of fibrin degradation products (REID & NKRUMAH, 1972) have been demonstrated in patients with cerebral malaria. An association between disseminated intravascular coagulation and acute pulmonary oedema has been suggested (PUNYAGUPTA *et al.*, 1974), but the high incidence of bleeding in these patients may have been related to coexistent uraemia (all cases), and treatment (heparin, low molecular mass dextran and dexamethasone). Platelet deposition was not seen, and fibrin was rare in the cerebral capillaries of fatal cases of cerebral malaria (MACPHERSON *et al.*, 1985). These data suggest that disseminated intravascular coagulation is probably not an important pathophysiological mechanism in severe malaria. Consumptive coagulopathy is usually low grade, but in a small proportion of cases it may become clinically important.

Significant bleeding occurs in approximately 5% of adult patients with cerebral malaria (PHILLIPS *et al.*, 1986a). A prospective study of coagulation indices confirmed that concentrations of fibrin degradation products were elevated in some patients, but this was usually in association with elevated fibrinogen and factor VIII concentrations, and low antithrombin III levels (PHILLIPS *et al.*, 1986a).

Several sensitive indices of intravascular coagulation, including decreased plasma antithrombin III concentration and activity and increased serum concentrations of thrombin–antithrombin III complexes, were proportional to disease severity but were abnormal even in patients with mild malaria (PUKRITTAYAKAMEE *et al.*, 1989).

Thrombocytopenia is a feature of falciparum and vivax malarias. It is sometimes profound in patients with severe disease, but this is not consistent enough to be of prognostic significance (PHILLIPS *et al.*, 1986a; HORSTMANN *et al.*, 1981). Possible causes include reduced platelet survival from intravascular lysis (by immune or other mechanisms, or consumption [disseminated intravascular coagulation]), enhanced splenic uptake or sequestration, and decreased platelet production.

Platelet survival is reduced to 2–4 d in severe falciparum malaria (SKUDOWITZ *et al.*, 1973; HORSTMANN *et al.*, 1981). Destruction by anti-platelet IgG antibodies was suggested by KELTON *et al.* (1983), who found increased platelet-associated IgG and IgG binding via the Fab terminus to platelet-associated malaria antigen. However, LEE *et al.* (1982) found no relationship between high-level IgG coating of platelets or antibody directed against the platelet surface and thrombocytopenia, nor any consistent change in these measures after resolution of thrombocytopenia. MOHANTY *et al.* (1988) found an inverse relationship between serum anti-platelet IgG antibody and platelet count in patients with malaria, suggesting an immune mechanism. However, studies in Thailand showed no relationship between platelet-bound IgG and platelet counts, and in particular thrombycytopenia was seen to resolve in the presence of unchanged antibody binding. In a murine model, thrombocytopenia was the result of peripheral destruction by an immune mechanism involving $CD34^+$ T lymphocytes and anti-platelet IgG antibodies (GRAU *et al.*, 1988). Although there is evidence of mild activation of intravascular coagulation in malaria of all grades of severity, this is insufficient to explain thrombocytopenia.

Transient increases in the numbers of marrow megakaryocytes in malaria were described by SRICHAIKUL *et al.* (1967). In Gambian children with acute malaria, there was an increase in numbers of megakaryocytes and megakaryoblasts in some cases (S. Abdulla, personal communication). C. J. Canfield (personal communication) noticed large, abnormal-looking megakaryocytes in the marrows of American servicemen with malaria in Viet Nam. These appearances suggested maturation arrest. In non-immune European patients with malaria, KNÜTTGEN (1987) found conspicuously increased numbers of megakaryocytes in all stages of development. Their abnormal morphology suggested highly stimulated proliferation (as an idiopathic thrombocytopenic purpura) and raised the possibility of dyspoietic thrombopoiesis as a contributing cause for thrombocytopenia. Circulating platelets appear abnormal in malaria. FAJARDO & RAO (1971) described enlarged platelets, up to 7·2 μm maximum diameter, in patients with falciparum and vivax malarias. Ultrastructural changes in the platelets of Indian patients with falciparum malaria included centralization of granules or degranulation and suggested *in vivo* activation (MOHANTY *et al.*, 1988). Platelets may be invaded by malarial parasites.

Platelet function has been studied in falciparum and vivax infections (reviewed by SRICHAIKUL *et al.*, 1988). Evidence of platelet activation *in vivo* includes an increase in the β thromboglobulin to platelet factor 4 ratio and elevated thromboxane B2 levels (SADAYASU *et al.*, 1991). Increased and decreased platelet aggregation in response to adenosine diphosphate, adrenaline, collagen and ristocetin have been described, and clot retraction was defective. These abnormalities were most marked in patients with severe falciparum malaria who had systematic complications and bleeding (SRICHAIKUL *et al.*, 1988).

Renal dysfunction

The mechanism of acute tubular necrosis in malaria, a complication virtually confined to adults, is not yet understood (SITPRIJA, 1988). Cytoadherence of parasitized red cells in the glomerular capillaries is occasionally seen, but is not as pronounced as in other organs such as the brain (MACPHERSON *et al.*, 1985; F. N. Turner, personal communication). Many patients are dehydrated when first admitted to hospital and in some of them renal function is restored to normal by simple rehydration. In patients with severe malaria, particularly those with hyperparasitaemia, jaundice or haemoglobinuria, renal impairment may persist despite rehydration. The clinical and biochemical pattern is of ischaemic nephropathy or acute tubular necrosis (TRANG *et al.*, 1992). Studies of renal cortical blood flow (^{133}Xe clearance method) (SITPRIJA *et al.*, 1977) and radiological studies (angiography and contrast urography) (ARTHACHINTA *et al.*, 1974) have shown a reduction in cortical perfusion during the acute stage of disease, as in other forms of acute tubular necrosis. Increased blood viscosity and hypovolaemia were considered contributory. The literature on renal abnormalities in malaria has been dominated by discussion of glomerular lesions and the concept of immunopathy (BOONPUCKNAVIG & SITPRIJA, 1979). However, most patients with acute renal failure in malaria have little or no proteinuria and a urinary sediment containing occasional granular and hyaline casts but no red cell cast. The absence of hypertension, the rapid resolution without residual impairment, and the predominance in adults rather than in children, together with the urinary sediment findings, all suggest that renal failure results from acute tubular necrosis and not glomerulonephritis (TRANG *et al.*, 1992). In view of the intense malarial antigenaemia it is not surprising that the kidney should show histopathological evidence of immune complex glomerulonephritis and mesangial and endothelial cell proliferation associated with deposition of immunoglobulin detectable by immunofluorescence and electron microscopy. In patients, glomerulonephritis may be a rare late development but seems unlikely to play any part in the development of acute renal failure.

Fluid balance

'Fluid compartmentalization' has been studied in both moderately and severely ill patients (MALLOY *et al.*, 1967). Plasma volume may be low on admission to hospital but after rehydration it is increased in the acute phase of the disease (FELDMAN & MURPHY, 1945; CHONGSUPHAJAISIDDHI *et al.*, 1971; WARRELL *et al.*, 1988). Total body water and extracellular volume (=sulphate space) tended to be increased. These findings, together with the haemodynamic observations and the reported elevation of plasma renin activity and aldosterone, and indices suggestive of increased antidiuretic hormone secretion (MALLOY *et al.*, 1967), all suggest that plasma volume increases to maintain effective circulating blood volume in the presence of generalized vasodilatation and falling haematocrit (BROOKS *et al.*, 1967). The high plasma volume is also a predictable result of anaemia. Similar observations have been made in other febrile illnesses.

Hyponatraemia

Hyponatraemia has been attributed to inappropriate secretion of antidiuretic hormone (MILLER, L. H. *et al.*, 1967; OGUNYE & GBADEBO, 1981; HOLST *et al.*, 1994) but, in Thailand, R. E. Phillips and others (personal communication) found that antidiuretic hormone levels were appropriate to serum osmolality in patients who were clinically hypovolaemic and, in some cases, salt depleted. Hypovolaemia results from fluid loss (fever, hyperventilation, vomiting, diarrhoea) and reduced intake of fluid. Hyponatraemia might arise in a patient who has sweated profusely for several days and drunk only water, or when a dehydrated patient is given intravenous dextrose solution.

Pulmonary oedema

The cause of this lethal manifestation of severe falciparum malaria is unknown. In many respects it resembles the adult respiratory distress syndrome. Several reported cases of acute pulmonary oedema probably resulted from over-enthusiastic administration of fluids (HALL, 1976, 1977), and the prevalence of the condition appears to have fallen since then. Patients with severe falciparum malaria may be particularly susceptible to acute pulmonary oedema from over-hydration. However, there is no doubt that acute pulmonary oedema can develop in patients who have not been over-hydrated; in these cases pulmonary capillary wedge pressures have been normal when measured (FEIN *et al.*, 1978; FELDMAN & SINGER, 1978; MARTELL *et al.*, 1979; N. P. J. Day & N. J. White, personal communication). Haemodynamic studies in severe malaria suggest a reduction in systemic vascular resistance and pulmonary vascular resistance but no clear relationship between pulmonary oedema and pulmonary artery occlusion pressure (CHAROENPAN *et al.*, 1990; DAY *et al.*, 1996). These results suggest that oedema can result from an increase in pulmonary capillary permeability. Pulmonary oedema often develops rapidly several days after appropriate chemotherapy has started. Thus, the pathophysiology may be different from that of the other severe manifestations of falciparum malaria. Ultrastructural studies of the lung have so far failed to give helpful clues to its aetiology (DUARTE *et al.*, 1985; MACPHERSON *et al.*, 1985), but the presence of large numbers of neutrophils lining the walls of small vessels is reminiscent of the effects of endotoxin.

Cardiovascular abnormalities, shock, 'algid malaria'

Myocardial function is remarkably good in severe falciparum malaria (WHITE, 1986; CHAROENPAN *et al.*, 1990; N. P. Day, personal communication). Most patients have an elevated cardiac index (>5 L/min/m^2) attributable to pyrogen-mediated vasodilatation with low systemic vascular resistance and low or normal pulmonary arterial wedge pressures (CRANSTON, 1966; WHITE, 1986). These changes are similar to those recorded in sepsis, although hypotension is less prominent in severe malaria (N. P. Day, personal communication). Some patients are clinically hypovolaemic on admission because of reduced fluid intake, and increased losses resulting from high fever, sweating and, in some patients, vomiting and diarrhoea.

Animal studies have indicated abnormalities in visceral perfusion which in some cases were reversible by α blockade (SKIRROW *et al.*, 1964), which suggests an arteriolar site of vascular obstruction. Primary myocardial dysfunction is rare in severe malaria, and cardiac arrhythmias are very uncommon (BETHELL *et al.*, 1996). There is usually an agonal fall in cardiac index but this appears to be secondary to metabolic acidosis, hypoxaemia and, in some cases, septicaemia (WHITE, 1986).

Orthostatic hypotension. Orthostatic hypotension is considered a frequent complication of falciparum malaria, occurring in 53% of cases before therapy (BROOKS *et al.*, 1967). This may be profound in uncomplicated infections although it is not clear whether it is more frequent in malaria than in other febrile illnesses of similar severity. Quinine and other quinoline antimalarial drugs exaggerate this phenomenon (SUPANARANOND *et al.*, 1993). The orthostatic hypotension is accompanied by a failure of compensatory reflex cardioacceleration, implying autonomic nervous system dysfunction (BUTLER & WEBER, 1973; SUPANANARANOND *et al.*, 1993). Possible mechanisms also include decreased vascular tone or cardiac output and reduced effective circulating blood volume (BROOKS *et al.*, 1967).

The shock-like state epitomized by the term 'algid malaria' is often associated with clinical and pathological evidence of gastrointestinal tract involvement. The clinical picture is reminiscent of Gram-negative septicaemia, and Gram-negative organisms have been cultured from the blood of these patients (see p. S1/17). Secondary Gram-negative septicaemias complicate other conditions in which there is a heavy intravascular infection or haemolysis, for example sickle cell disease, bartonellosis and relapsing fevers. Endotoxaemia has been detected by the limulus assay in patients with falciparum malaria in the absence of demonstrable bacterial infection (TUBBS, 1980; AUNG-KYAW-ZAW *et al.*, 1988); it increases in prevalence with increasing parasitaemia (USAWATTANAKUL *et al.*, 1985). The most likely explanations are cross reaction with malarial 'toxins' or passive absorption of endotoxin from the gut lumen resulting from cytoadherence of parasitized erythrocytes in small blood vessels in the villi leading to ischaemic damage to the epithelium. Many of the damaging effects of endotoxin are now identified with cachectin (TNF), a protein produced by endotoxin-activated macrophages (TRACEY *et al.*, 1986) in response to viral, bacterial and protozoal infections.

Gastrointestinal disturbances

Nausea and vomiting are common in malaria, particularly in children with high fever. Vomiting may be provoked by antimalarial drug treatment, of particular concern when single dose antimalarial compounds are given such as mefloquine or sulphadoxine/pyrimethamine. Diarrhoea has been reported in some geographical areas but appears to be very unusual in others; the pathogenesis is not understood. Although malabsorption of amino acids, sugars, fats, chloroquine and quinine have been documented, in most studies oral absorption of antimalarial drugs in uncomplicated malaria has been normal in even the most seriously ill patients (OLSSON & JOHNSTON, 1969; KARNEY & TONG, 1972; SENGAL, H. E. *et al.*, 1974; HERZOG *et al.*, 1982; CHANTHAVANICH *et al.*, 1985; WHITE *et al.*, 1988b, 1989). In the acute phase of severe falciparum malaria, Thai patients showed greatly reduced absorption of sugars which rely on mediated mechanisms and unmediated diffusion. Absorption returned to normal in convalescence. The pattern of reduced absorption was not characteristic of mucosal damage but could have resulted from impaired splanchnic perfusion. Liver blood flow, which is also affected by splanchnic perfusion, was concomitantly reduced in severe malaria (MOLYNEUX *et al.*, 1989a). Biopsies of the gut indicate parasite sequestration in the vascular bed which presumably interferes with the absorptive process (DUDGEON & CLARK, 1917; DANIELS & NEWHAM, 1923). Endotoxaemia may also originate from the gut, by entry of either Gram-negative bacteria or endotoxin from the gut lumen and failure of the normal hepatic clearance mechanisms (USAWATTANAKUL *et al.*, 1985). There are rare reports of acute pancreatitis complicating falciparum malaria (MASHAAL, 1986; GURMAN *et al.*, 1988).

Hypoglycaemia

Hypoglycaemia is increasingly recognized as an important manifestation of falciparum malaria. There are several possible causes of hypoglycaemia and different patterns of associated biochemical abnormalities.

Quinine/quinidine-induced hyperinsulinaemia. Quinine is a most potent stimulus *in vitro* to islet cell insulin secretion (HENQUIN *et al.*, 1975) and has been shown to release insulin *in vivo* in healthy subjects and in patients with falciparum malaria, in both pregnant women with severe or relatively mild disease and adults and children with severe disease (WHITE *et al.*, 1983a; LOOAREESUWAN *et al.*, 1985a; OKITOLONDA *et al.*, 1987; DAVIS *et al.*, 1991; KRISHNA *et al.*, 1994a). Insulin release can be attenuated by lipid infusions which increase free fatty acid concentrations (DAVIS *et al.*, 1995) or inhibited by somatostatin (PHILLIPS *et al.*, 1993).

Increased glucose consumption. Glucose consumption

increases in fever and infection. Increased glucose turnover in acute falciparum malaria results from increased glucose consumption both by the host and the parasite (DAVIS *et al.*, 1988a, 1993b) although the host's requirements are considerably greater. Lactic acidosis commonly coexists with hypoglycaemia, and lactate turnover is increased in severe malaria with a switch from skeletal muscle consumption to production (DAVIS *et al.*, 1995). Hypoglycaemia (SADUN *et al.*, 1965) and lactic acidosis are also common in the terminal phases of the lethal animal malarias (KRISHNA *et al.*, 1983). Lactate accumulation results when production from host and parasite anaerobic glycolysis exceeds hepatic clearance (DAVIS *et al.*, 1995). Glucose consumption and lactate production by malaria parasites have been studied *in vitro*, and found to be proportional to the stage of parasite development (PFALLER *et al.*, 1982; JENSEN *et al.*, 1983; ZOLG *et al.*, 1984). The overall metabolic contribution from the parasite biomass *in vivo* in falciparum malaria cannot be calculated accurately in the absence of methods for estimating the number of parasites in the body. However, rough calculations suggest that, at high parasite burdens (heavy infections with relatively synchronous mature parasites), parasite glycolysis could contribute significantly, although the main cause of hypoglycaemia and lactic acidosis would still be increased glucose consumption coupled with reduced gluconeogenesis in the host. This imbalance between glucose supply and demand may be accentuated in tissues where mature parasites are adherent to the vascular endothelium of capillaries and venules and blood flow is low.

Glycogen depletion or impaired gluconeogenesis. Hypoglycaemia in African children with severe malaria, and in adults who have not received previous quinine treatment, is associated with appropriately low plasma concentrations of insulin (WHITE *et al.*, 1983a, 1987a; LOOAREESUWAN *et al.*, 1985a; TAYLOR *et al.*, 1988; KRISHNA *et al.*, 1994a). Hypoglycaemia is associated with elevated concentrations of lactate and alanine and a moderate increase in ketone body concentrations (WHITE *et al.*, 1987a; TAYLOR *et al.*, 1988). Counterregulatory hormone levels are appropriately raised (TAYLOR *et al.*, 1988). Hypoglycaemia is considered to result from variable depletion of hepatic glycogen, inhibition of hepatic gluconeogenesis, and a 2–3-fold increase in glucose turnover (DAVIS *et al.*, 1993b). Fasting reduces glycogen stores rapidly even in well-nourished children, but high substrate levels (lactate and alanine) and absence of ketosis in many hypoglycaemic children suggest that other factors are involved in addition to starvation. An identical pattern of biochemical and hormonal disturbances has been observed in Bangladeshi children with hypoglycaemia associated with dysentery (PHILLIPS *et al.*, 1988).

Lactic acidosis

Lactic acidosis is a major cause of death from severe falciparum malaria (WHITE *eta l.*, 1983a, 1987a; TAYLOR *et al.*, 1988, 1993; KRISHNA *et al.*, 1994a). Metabolic acidosis is a consistent feature of severe malaria in adults and children (MARSH *et al.*, 1995), and in children this is mainly lactic acidosis, whereas in adults renal failure and lactic acidosis both contribute. Lactate, measured in either venous or arterial blood or in cerebrospinal fluid, is an accurate prognostic indicator in severe malaria (WHITE & HO, 1992; WALLER *et al.*, 1995). Elevated concentrations of lactic acid in the blood result from tissue anaerobic glycolysis, particularly in skeletal muscle (DAVIS *et al.*, 1995) and possibly also the gut. There appears to be a failure of the usual pathways of hepatic and renal metabolic clearance of lactate which leads to its accumulation. Liver blood flow has been shown to be closely related to hyperlactaemia; plasma lactate concentrations rise progressively with flows <15 mL/kg/min (PUKRITTAYA-KAMEE *et al.*, 1994). Lactic acid levels rise rapidly following generalized convulsions and this may be a compounding factor. The pharmacological activator of pyruvate dehydrogenase, dichloroacetate, has been shown to be beneficial in an animal model of malaria-induced lactic acidosis, and preliminary studies in humans are encouraging (KRISHNA *et al.*, 1994a, 1994b; HOLLOWAY *et al.*, 1995). High blood lactate levels also result from decreased liver blood flow (PUKRITTAYAKAMEE *et al.*, 1994).

Other metabolic abnormalities

In children with cerebral malaria the plasma levels of non-essential fatty acids (NEFA) are elevated, the highest concentrations being found in patients with pretreatment hypoglycaemia (T. E. Taylor, and M. E. Molyneux, personal communication). This elevation probably results both from increased lipolysis and impaired hepatic lipoprotein synthesis. Serum triglyceride levels are also elevated in animals (ANGUS *et al.*, 1971) and children with severe malaria (M. E. Molyneux & T. E. Taylor, personal communication), possibly as a result of impaired lipogenesis. It is possible that both the hepatic and lipogenic defects may be mediated by TNF or other cytokines.

Rhabdomyolysis

Skeletal muscle necrosis was reported in a 17 years old man with severe falciparum malaria who developed myoglobinuria and acute renal failure (DE SILVA *et al.*, 1988). In a study of West African children with malaria, creatinine kinase and myoglobin levels in plasma were elevated in children with altered consciousness and were significantly higher in unrousable than in rousable children (MILLER, K. D. *et al.*, 1989a). The possibility that skeletal muscle is an important site of sequestration should be more fully investigated.

Pregnancy

Falciparum malaria in pregnancy carries a high mortality rate for the fetus and in areas with low communal immunity also for the mother (BRAY & ANDERSON, 1979; LOOAREESUWAN *et al.*, 1985a). Histopathological changes in the malarious placenta include excess intervillous macrophages, perivillous fibrin deposits stained with malarial pigment, fibrinoid necrosis of the chorionic villi, and thickening of the trophoblast basement membrane, which may be responsible for placental insufficiency (PHILIPPE & WALTER, 1985; ANAGNOS *et al.*, 1986; YAMADA *et al.*, 1989; BULMER *et al.*, 1993a, 1993b) and reduced maternal–fetal transfer (Brair *et al.*, 1994).

TERRY (1988) stated that certain sites such as the eye, brain and testes are recognized as being immunologically privileged and suggested that certain parts of the blood microcirculation may be privileged sites for parasites. Such sites may permit the persistence of *P. falciparum* and the placenta could be, at least in part, a privileged site. Immune processes in the placenta are qualitatively and quantitatively different from those in the remainder of the body (RASHEED *et al.*, 1993).

The placenta certainly appears to be a site of preferential parasite sequestration and development. This presumably interferes with transplacental delivery of nutrients to the fetus. As in other vascular beds, microcirculatory obstruction and competition for metabolic substrates may both contribute. Acute placental insufficiency is the net result and in areas of unstable transmission, where symptomatic disease in the mother is common, fetal distress is commonly undiagnosed and the mortality is high. The mother appears to be particularly likely to develop acute pulmonary oedema and hypoglycaemia (WHITE *et al.*, 1983a). Hypoglycaemia is more common than in normal pregnancies because of the accelerated response to starvation and increased glucose turnover (DAVIS *et al.*, 1994). In addition, the

pancreatic islet cells in pregnancy are functionally hyperresponsive to secretagogues such as quinine (LOOAREESUWAN *et al.*, 1985a). These factors, combined with the metabolic demands of the infection, probably render pregnant women more vulnerable to hypoglycaemia.

In areas of high transmission, pregnancy increases the risk and density of peripheral *P. falciparum* parasitaemia; placental parasitaemia is common and is associated with low birth weight, especially in first and second pregnancies. Malaria in this setting does not appear to be an important cause of severe maternal disease, fetal loss or maternal and perinatal mortality (see p. S1/19). In non-immune populations, pregnancy increases the risk of severe maternal disease, fetal loss, premature delivery and perinatal mortality.

Altered immunity in pregnancy. It is not clear whether natural immune depression during pregnancy or factors associated with the placenta encourage parasite multiplication and clinical manifestations. VLEUGELS *et al.* (1987) found that pregnant women with malaria in Tanzania had significantly higher total and free serum cortisol concentrations than control women without malaria, whether nulliparous or multiparous. This was consistent with the pattern seen in a murine model (VON ZON *et al.*, 1982, 1985). However, a non-specific effect of infection on cortisol level was not adequately excluded by these investigators. In Gabon, GARIN *et al.* (1985) found that parasitaemia and placental changes were more frequent in first and second pregnancies than in subsequent ones, and were associated with a decrease in antibodies inhibitory to merozoite invasion at the time of delivery. Proliferative responses of both placental and peripheral lymphocytes to malarial antigens are lower in Gambian primigravidae than in multigravidae, despite similar antimalarial antibody levels (RASHEED *et al.*, 1993).

M. Hommel (personal communication) suggested in 1995 that the placental site offers a haven for parasites of a phenotype that cannot normally flourish in a semi-immune host; with later pregnancies the effect is diminished because each pregnancy boosts immune responses to the 'placental phenotype'. The mechanism of accumulation of parasites in the placenta is not known: parasitized erythrocytes do not appear to be cytoadherent to host endothelial cells, as is usual in other sequestration sites (BRAY & SINDEN, 1979; WALTER *et al.*, 1982). A distinct subpopulation of malaria parasites, that bind to chondroitin sulphate A rather than to CD36, may be involved in placental sequestration (FRIED & DUFFY, 1998).

Placental pathology. Histopathological changes in the malarious placenta include excess intervillous macrophages and perivillous fibrin deposits stained with malarial pigment (PHILIPPE & WALTER, 1985; ANAGNOS *et al.*, 1986). Other placental changes that accompany parasite sequestration are focal necrosis of the trophoblast, partial loss of microvilli and thickening of the trophoblastic basal membrane (YAMADA *et al.*, 1989).

The mechanism by which placental parasitization affects fetal growth is unknown. Actively metabolizing parasites may deprive the fetus of nutrients, pathological changes in the placenta may affect its function, or the release of cytokines into the fetal circulation may influence fetal metabolism.

The recent finding that *P. vivax* malaria also reduces birth weight questions the role of local placental sequestration in the pathophysiology of intra-uterine growth retardation in malaria (F. Nosten, personal communication).

Hypoglycaemia. In non-immune pregnant women with malaria, hypoglycaemia can be both pregnancy-related and quinine-induced.

Hypoglycaemia may develop in normal pregnancies because there is an accelerated response to starvation: there is β-cell hyperplasia in the pancreatic islets, and basal and post-prandial insulin concentrations are raised (LANDON & GABBE, 1988). In non-pregnant patients with severe malaria, glucose turnover is accelerated by about 50% (DAVIS *et al.*, 1993), and there is a similar increase in association with uncomplicated malaria in the second and third trimesters of pregnancy (DAVIS *et al.*, 1994). These observations may account for the increased incidence of hypoglycaemia associated with malaria in pregnancy.

Pancreatic islet cells in pregnancy are functionally hyperresponsive to secretagogues such as quinine. In a study of pregnant Thai women with malaria and hypoglycaemia, plasma insulin concentrations were inappropriately high and quinine-induced hyperinsulinaemia appeared to be a likely mechanism of hypoglycaemia (WHITE *et al.*, 1983a).

Diagnosis of malaria

Clinical diagnosis of severe malaria

Both in residents of malaria-endemic areas, and in travellers from such regions, malaria must be considered in the differential diagnosis of any fever. Malaria can present with a wide range of symptoms and signs, none of them in any way specific.

Discovery of parasitaemia can quickly confirm clinical suspicion of malaria, but, in patients with symptoms compatible with severe disease, a therapeutic trial of parenteral antimalarial drugs is justified, even if the initial blood film is negative.
This applies both to presumed non-immune patients with suspected imported malaria in 'western' countries and, in endemic areas of Africa, to severely ill patients.

Asymptomatic parasitaemia may be common in endemic areas, but the discovery of parasitaemia in severely ill patients should be an indication for urgent antimalarial treatment. However, other causes of the symptoms should be sought and, depending on the clinical features, it may be appropriate to cover common bacterial infections (e.g., meningitis, septicaemia and pneumonia) as well.

Differential diagnosis. The clinical diagnosis of severe malaria can be difficult for the following reasons.

(i) There is no component of the clinical picture of malaria or its complications that is unequivocally diagnostic of the infection; all features can be mimicked by other diseases.

(ii) The presence of parasitaemia does not prove that malaria is the main or only cause of a patient's illness, especially in endemic areas where asymptomatic parasitaemia may be common in those who have developed immunity.

(iii) Conversely, patients with severe malaria are occasionally seen whose blood film at the time of presentation is negative because of previous treatment, a highly synchronous infection, or comprehensive sequestration of parasitized erythrocytes in deep vascular beds. Repeated blood films usually reveal the diagnosis, but treatment should not be delayed if there is reasonable suspicion that the patient is suffering from malaria; i.e., if the patient has been exposed to *P. falciparum* infection within the past year and has symptoms and signs of severe disease.

A number of other diseases and conditions should be considered in the differential diagnosis of a patient in whom severe malaria is suspected (Table 6). The geographical, occupational or travel history may point to increased likelihood of one of these diagnoses. In children, febrile convulsions or hypoglycaemia can complicate any fever, and the clinical picture may resemble cerebral malaria. Reye's syndrome has many features in

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Table 6. Differential diagnosis of severe malaria

Symptom	Diagnosis
Acute fever	Fever due to other infections, heat stroke, drugs and other causes In pregnant or post-partum women: infection of urinary tract, uterus, adnexa, breast
Paroxysms (rigors)	Other infections, especially lobar pneumonia, ascending cholangitis, pyelonephritis and viral hepatitis; acute intravascular haemolysis
Confusion, obtundation, coma ('cerebral malaria')	Viral, bacterial, fungal (e.g., cryptococcal), protozoal (e.g., African trypanosomiasis) or helminthic meningoencephalitis Cerebral abscess Head injury, intracranial bleed/thrombosis/embolism Intoxications and poisonings (e.g., antimalarial drugs, insecticides, herbicides) Metabolic (diabetes, hypoglycaemia, uraemia, hepatic failure, hyponatraemia) Septicaemias, 'cerebral' typhoid
Convulsions	Encephalitides, metabolic encephalopathies, hyponatraemia, hyperpyrexia, heatstroke, cerebrovascular accidents, epilepsy, drug and alcohol intoxication or withdrawal, poisoning In pregnant women: eclampsia, listeriosis In children: febrile convulsions, Reye's syndrome
Bleeding/clotting abnormalities	Septicaemias (e.g., meningococcaemia), viral haemorrhagic fever, rickettsial infection In pregnant women: post-partum defibrination syndrome
Abnormal behaviour ('malaria psychosis')	Psychosis, alcohol intoxication/withdrawal, other drugs (including antimalarial drugs such as mefloquine) and poisons, viral encephalitis (e.g., *Herpes simplex*, rabies, etc.)
Jaundice	Viral hepatitis, yellow fever, leptospirosis, relapsing fevers, septicaemias, haemolysis, biliary obstruction, hepatic necrosis (drugs, poisons) In pregnant women: acute fatty liver, cholestasis In neonates: rhesus incompatibility, other intrauterine infections (e.g., cytomegalovirus, *Herpes simplex*, rubella, toxoplasmosis, syphilis)
Nausea, vomiting, diarrhoea ('bilious remittent fever')	Travellers' diarrhoea, dysentery, enteric fever, other bacterial infections, inflammatory bowel disease
Abdominal pain	Ruptured spleen, enteric fevers, amoebic liver abscess, acute pancreatitis, perforation, peritonitis In women of reproductive age: ruptured ectopic pregnancy
Haemoglobinuria ('blackwater fever')	Drug-induced haemolysis (e.g., oxidant antimalarial drugs in G-6PD-deficient patient), favism, transfusion reaction, dark urine of other causes (e.g., myoglobin, urobilinogen, porphobilinogen)
Acute renal failure	Septicaemia, yellow fever, leptospirosis, drug intoxication, poisoning, prolonged hypotension
Shock ('algid malaria')	Septicaemic shock, haemorrhagic shock (e.g., massive gastrointestinal bleed, ruptured spleen), perforated bowel, dehydration, hypovolaemia, myocarditis

Table 7. Similarities between cerebral malaria in African children and Reye's syndrome in American children[a]

	Cerebral malaria	Reye's syndrome
Age (years)[b]	3 (0·5–8)	11 (1–19)
Male:female ratio	1:1	1:3·2
Prodromal illness	2–3 d of fever	In 76–100%
Fever on admission	>99%	?
Vomiting	55%	95%
Seizures	50%	50–72%
Brainstem signs	34%	38%
Papilloedema	Rare	Rare
Hypoglycaemia	23%	5·25%
Metabolic acidosis	42%	100%
Severe anaemia	46%	0
Sequelae	11%	10–15%
Death	15%	43–62%

[a]NEWTON (1994).
[b]Median (range in parentheses).

common with cerebral malaria but is distinguished by hepatic involvement (fatty infiltration) and cerebral oedema (NEWTON, 1994) (Table 7). During pregnancy and the puerperium, severe malaria must be distinguished from sepsis arising in the uterus, urinary tract or breast. Cerebral malaria is usually distinguishable from eclampsia, which has other features (hypertension, oedema, etc.). The presence of a rash, lymphadenopathy, or any sign of focal infection in a patient with suspected malaria should suggest a different or additional diagnosis.

In temperate countries, the possibility of malaria in returning travellers is often ignored. Severe malaria may be misdiagnosed as 'influenza', encephalitis, hepatitis, enteric fever, or psychosis, and the diagnosis of malaria may be missed in patients presenting with acute renal failure, a bleeding diathesis, severe haemolysis, pulmonary oedema, or shock. Heat stroke should be considered in the differential diagnosis of severe fever and altered consciousness, especially in unacclimatized visitors to the tropics or if there is a history of excessive exercise. Some patients with malaria develop diarrhoea, which may be profuse and watery suggesting cholera, and occasionally may be bloody and may be mistaken for dysentery or gastroenteritis.

Parasitological diagnosis

One of the four technical elements of the Global Malaria Control Strategy (WHO, 1993a) is to provide early diagnosis and prompt treatment. However, in the implementation of this strategy (WHO, 1993b) it was recognized that laboratory support for the diagnosis of malaria may be of limited value for adults and, to some extent, for children in highly endemic areas, because of the high prevalence rate of asymptomatic parasite carri-

ers. Nevertheless the exceptions are severe disease, treatment failures and uncomplicated malaria during the low transmission season. The principle is that patients everywhere who are suspected of having malaria must receive full treatment without delay. Laboratory diagnosis should be used primarily as a support for clinical care. With the increasing problem of drug-resistant malaria in areas with *P. falciparum*, the capacity to examine blood microscopically needs to be available as far into the periphery of the health service as feasible and the technique should be incorporated into patient management as soon as possible.

There is a correlation between density of parasitaemia and severity of malaria. Studies in Malaysia (FIELD & NIVEN, 1937) showed that the death rate in falciparum infections rose steeply as the parasitaemia exceeded 100 000/μL of peripheral blood. There was approximately 1% mortality with parasite counts below 100 000/μL, rising to more than 50% with counts exceeding 500 000/μL. Thus, in areas where malaria is of low endemicity, patients with *P. falciparum* parasitaemia above 100 000/μL (above 250 parasites per thick blood film field or 2% infected erythrocytes) warrant careful observation, especially if the haematocrit is low. The presence of late trophozoites and schizonts of *P. falciparum* in peripheral blood is also a sign of risk of severity. Children in areas of stable endemicity may tolerate very high levels of parasitaemia without severe symptoms but, in children with cerebral malaria, parasitaemias in excess of 1 000 000/μL were significantly associated with a fatal outcome (MOLYNEUX *et al.*, 1989b).

While high parasite densities can be equated with severity, the reverse is not always true, particularly in non-immune individuals. In *P. falciparum* infections the density of parasitaemia as measured in the peripheral circulation may wax and wane. Parasitaemia may fluctuate widely in the first 24 h of treatment, and may rise alarmingly despite the administration of adequate antimalarial drugs. The relationship between peripheral circulating erythrocytes infected with ring forms of the parasite and sequestered infected cells is a function (predominantly) of the stage of development (synchronicity) and, to a much lesser extent, the parasite multiplication rate (WHITE *et al.*, 1992). There may be wide differences between the number of infected cells circulating and the number sequestered, and rapid changes may be expected in synchronous infections (WHITE & KRISHNA, 1989). Thus, it is important to examine serial blood films at intervals of 6 to 12 h. Self-medication or chemosuppression may reduce parasitaemia to below the detectable threshold. Serial blood films are required as long as the diagnosis remains in doubt and to monitor response to specific chemotherapy.

In both the situations mentioned above, the presence of malaria pigment in neutrophils and monocytes is a useful indication of the diagnosis of malaria, and it should always be looked for. The quantity of malaria pigment liberated into the circulation at schizogony reflects the pathogenic sequestered parasite burden in *P. falciparum* malaria, and may therefore be a measure of disease severity (PHU *et al.*, 1995). Among 300 consecutive adult patients with severe falciparum malaria, studied by PHU *et al.* (1995) in Viet Nam, the 40 who died had significantly higher proportions of malaria pigment-containing neutrophils on admission and pigment-containing monocytes than did survivors. This proved a better indicator of prognosis than the peripheral parasite count.

The presence of malaria parasites in the blood may be detected by routine microscopical examination of thick blood films when densities are of the order of 5 to 10 parasites/μL of blood, provided 100 microscope fields are examined by a competent microscopist. If thick blood films are made properly, 100 oil immersion fields are equivalent to about 0·25 μL of blood.

Thick films are more useful than thin films in the detection of low parasitaemia. Their reliable examination requires a degree of technical precision in the preparation of the blood slide, its handling and staining, in the optical quality of the microscope and the illumination, as well as competence and care on the part of the microscopist. Malaria parasites may occasionally be discovered by examination of poorly prepared slides or in thin blood films prepared for differential blood cell counts, but falciparum rings at relatively low densities will have little chance of being found in that way.

The microscopical diagnosis of malaria parasites may be fraught with many pitfalls: e.g., artefacts are often mistaken for parasites (and good staining technique is required to reduce them to a minimum); Maurer's clefts may be confused with Schüffner's dots, causing *P. falciparum* to be diagnosed as *P. vivax*; *Babesia* and *Bartonella* infections may be mistaken for malaria; young gametocytes of *P. falciparum* may be mistaken for *P. vivax*. However, blood film examination remains the most valuable technique for diagnosis and monitoring of severe malaria. It is, however, essential that laboratory personnel are very well trained and undergo constant refresher training. Patients in whom there is a high clinical suspicion of severe malaria, and whose repeated blood films are negative for *P. falciparum*, could be tested using one of the available rapid manual tests that do not need a microscope, such as the *Para*Sight™-F test or the ICT Malaria Pf™ card test. These have not replaced microscopy as the standard method for the diagnosis of malaria, although the *Para*Sight™-F test can be made semi-quantitative and measurement of plasma PfHRP2* (as in the ICT Malaria Pf™ test) may be a useful measure of severity (DESAKORN *et al.*, 1997).

Patients with clinical evidence of severe disease but in whom only *P. vivax, P. malariae* or *P. ovale* is found in the peripheral blood film should be treated as if they had severe falciparum malaria. Mixed infections are underrecognized. In some countries seriously ill patients are commonly encountered who have received several days of antimalarial treatment before referral, and have negative blood films. This is another situation in which the rapid tests based on *P. falciparum* HRP2 may be useful, as a negative test does rule out severe malaria as a cause of illness.

The efficacy of the malaria chemotherapy being used needs to be monitored carefully and, for this, serial parasite counts are necessary in thick and thin blood films. Much can be gained in skilled hands from the examination of a thick blood film and, for the time being, this will have to continue. Facilities for managing severe disease must have well-trained laboratory personnel and appropriately equipped and supported laboratories.

Prognostic value of the peripheral blood film in severe falciparum malaria

The relationship between parasite count and the prognosis of falciparum malaria varies with background endemicity. At low levels of transmission, where there is little or no background immunity, parasite counts over 100 000/μL are associated with increased mortality (FIELD & NIVEN, 1937; FIELD, 1949). Above this threshold there is an increased risk with increasing levels of parasitaemia, but the predictive prognostic value of the parasite count is poor. Some individuals with high parasite counts may not be severely ill, whereas others with low parasitaemia may have ultimately fatal infections. In this epidemiological context the prognostic value of the blood film may be improved by the following 2 simple additional procedures.

(i) Assessment of the state of parasite development (SILAMUT & WHITE, 1993). In severe malaria, large numbers of red blood cells containing mature forms of the parasite are sequestered in the capillaries and

P. falciparum histidine-rich protein 2.

venules of vital organs. This explains the discrepancy between peripheral parasitaemia and severity; i.e., some patients may have most of their parasite biomass sequestered, and others may have most of their parasites circulating. However, the distribution of parasite stages in the peripheral blood does provide a clue to the numbers of sequestered parasites. Patients with more mature stages in the peripheral blood (best assessed in the thin film) are more likely to have a larger sequestered biomass. If more than 20% of the parasites contain visible malaria pigment (i.e., the parasites are mature trophozoites or schizonts), the prognosis is worse, whereas if >50% of the parasites are tiny rings (young parasites in which the thickness of the parasite cytoplasm opposite the nucleus is <50% of the width of the parasite nucleus), the prognosis is better.

(ii) Counting the proportion of peripheral blood polymorphonuclear leucocytes which contain visible malaria pigment (PHU *et al.*, 1995). This pigment is easily seen and appears as brown–black refractile material (like a piece of coal) within the polymorphonuclear cell's cytoplasm. Malaria pigment is released at schizogony, and therefore the amount released into the circulation reflects the number of parasites that have under-gone schizogony. As polymorphonuclear cells are short-lived in the circulation ($t_{1/2}$ about 9 h), the number of these cells which contain pigment is a more accurate reflection of recent schizogony than the number of monocytes containing pigment, as monocytes remain in the circulation for days rather than hours. In Vietnamese adults with severe falciparum malaria, the finding of ≥5% polymorphonuclear cells containing visible pigment was associated with a poor prognosis (PHU *et al.*, 1995). The prognostic sensitivity and specificity of these 2 assessments has not been determined extensively outside low transmission areas in south-east Asia, and could be different in areas of higher transmission. Nevertheless, these findings are likely to be applicable to non-immune patients with severe malaria. These microscopical assessments are easy to perform on the thin blood film, and the number of polymorphonuclear cells containing pigment can be counted more rapidly than parasites.

Chemotherapy of severe malaria

General considerations of chemotherapy

The various salts of quinoline compounds (cinchona alkaloids and related compounds such as mefloquine and halofantrine, 4-aminoquinolines and 8-aminoquinolines) contain greatly differing amounts of **base** (Annex 2). If the prescription fails to specify **salt** or **base**, or which particular salt is intended, serious problems of over- or under-dosing can arise. Whenever possible, the dose of **base** should be prescribed. This is generally accepted for mefloquine, chloroquine, amodiaquine and primaquine, but, in the case of quinine, quinidine and halofantrine, doses of salts are usually quoted.

Warning. The fact that antimalarial drugs may be prescribed as either *base* or *salt* (see Annex 2) has caused potentially dangerous confusion. Always double-check whether the dose refers to *base* or *salt*.

Diagnosis. Ideally, the species of malaria parasite, the parasite density and the geographical origin of the infection should be known. In patients with features of severe malaria, a mixed infection including *P. falciparum* should be assumed even if parasites of one of the benign species alone are identified in the blood film. A therapeutic trial is justified in patients who were exposed to infection and develop severe symptoms even if the blood film is consistently negative.

Details of the patient. Choice of treatment will depend on the age and genetic origin of the patient, their presumed immune status and, in the case of women, whether they are pregnant or lactating or not. Dose must be calculated from the patient's weight whenever possible.

Clinical condition. A patient's clinical condition is of great importance. Patients with severe falciparum malaria and those who are vomiting will require parenteral treatment at least during the initial phase of management.

Prior treatment. Some prior treatment is extremely common, particularly in developing countries where drugs such as chloroquine are sold across the counter for the treatment of fevers and suspected malaria. Malaria which breaks through prophylaxis (for example, with chloroquine) or which recrudesces or relapses after a recent course of chemotherapy is probably caused by a parasite resistant to that drug.

Although patients who have taken an antimalarial drug within the previous one or 2 days may develop toxic levels if the same drug is given again, the fact that they have developed severe malaria despite antimalarial treatment suggests that this drug was not adequately absorbed. In many areas the majority of patients admitted to hospital with severe malaria have already received some previous antimalarial treatment (SILAMUT *et al.*, 1995). Thus in practice, for all the antimalarial drugs used in severe malaria, full treatment doses should be given unless there is clear evidence of adequate pre-treatment. This is particularly relevant to quinine, the drug with the narrowest of the therapeutic ratios, where toxicity has not been encountered despite the use of full loading doses in patients who have received pre-treatment (TRAN *et al.*, 1996).

Objectives of chemotherapy. These will differ between mild and severe infections and in different geographical situations. In the treatment of uncomplicated infections in endemic areas, the main objective may be to produce symptomatic improvement; radical cure may be an unrealistic objective where early reinfection is almost certain. In severe malaria, which can kill the patient within a few days, parasiticidal plasma concentrations of the antimalarial drug must be achieved as quickly and as safely as possible and sustained for long enough to ensure rapid clearance of parasitaemia. Single dose regimens to ensure compliance, the prevention of recrudescences and the killing of gametocytes—which may be important considerations in the treatment of uncomplicated malaria in endemic regions—are of little importance in the treatment of severe disease. Symptoms which are troublesome to the fully conscious patient with uncomplicated malaria, such as cinchonism or pruritus, are acceptable in the treatment of life threatening disease and should not limit dosage.

Risk–benefit analysis. The choice of drugs for therapy and prophylaxis should depend on a proper assessment of the balance between the therapeutic needs and urgency in a particular case and the risks of toxicity.

Cost. Most malarious countries are relatively poor and so the choice of treatment will usually be determined by cost. In the UK at present the costs of some antimalarial drugs compared to chloroquine (=1) are as follows: quinine 7·5, mefloquine 36·3, halofantrine 23·3; and in the USA: mefloquine 19·2, halofantrine 53·1, Fansidar® 1·3. In some estimates made by WHO using European prices, the cost of a course of treatment relative to that of chloroquine (=1) were as follows: halofantrine 66·4, mefloquine 24·0, quinine 18·4, amodiaquine 1·75, Fansidar® 1·6. In general, parenteral treatment courses with the artemisinin derivatives cost either the same as, or slightly less than, quinine. Prices will vary greatly in different countries and brand-name antimalarial drugs are considerably more expensive than their generic equivalents on the international market.

Quinine

Quinine is currently the most widely used drug in the chemotherapy of severe falciparum malaria.

Formulation. Parenteral quinine is usually formulated as the dihydrochloride salt in concentrations of 60–300 mg/mL. It is readily photodegraded and should be stored in brown glass ampoules in the dark. Photodegradation is insignificant over short periods (i.e., <24 h) when quinine is dissolved in an infusion solution of 0·9% sodium chloride (normal saline) or dextrose (K. Silamut & N. J. White, personal communication). It is otherwise stable at room temperature for long periods. Quinimax® is a mixture of cinchona alkaloids (96·1% of quinine, 2·5% quinidine, 0·68% cinchonine and 0·67% cinchonidine), widely used in Francophone countries (also Quinoform®).

Administration. Intravenous quinine should be given by rate-controlled intravenous infusion. **It must not be given by bolus intravenous ('push') injection**. In severe malaria, previously untreated patients should be given an initial loading dose (WHITE *et al.*, 1983b). Where there are intensive care facilities, quinine may be given in an initial dose of 7 mg salt/kg over 30 min by infusion pump followed immediately by 10 mg salt/kg over 4 h (i.e., total dose 17 mg over 4·5 h) (DAVIS *et al.*, 1988b, 1990). Where this is not possible an initial infusion of 20 mg salt/kg should be given over 4 h (WHITE *et al.*, 1983b; TAYLOR *et al.*, 1988; PASVOL *et al.*, 1991). Neither of these regimens is associated with significant iatrogenic cardiovascular or nervous system toxicity, but there remains uncertainty about safe dosage at extremes of age and weight in some racial groups (BONINGTON *et al.*, 1996). BOELE VAN HENSBROEK *et al.* (1996a) have recently studied the pharmacokinetics and toxicity of quinine in Gambian children with severe malaria less than 2 years of age. Plasma concentrations were slightly higher and prolongation of the electrocardiogram ARS interval was significant compared with older children. The objective of a loading dose is to provide therapeutic blood concentrations as early as possible in the course of treatment without 'overshoot' to toxic levels. The loading dose is unnecessary if the patient has received more than 40 mg/kg of quinine in the previous 2 d. As pre-treatment is common in the tropics and the patient's history may be unreliable, there is often concern that administration of a loading dose may cause cumulative toxicity. In practice this is rare (TRAN *et al.*, 1996), so if in doubt the loading dose should be given. Use of a rapid dipstick method for quantitating quinine pre-treatment allows accurate assessment (SILAMUT *et al.*, 1995). Patients who have developed severe malaria despite treatment with mefloquine should be given the loading dose unless the last dose of mefloquine was administered within the previous 12 h.

The maintenance doses of quinine (10 mg salt/kg) should be infused at rates not exceeding 6 mg/kg/h (i.e., over 2 h).

A dose interval of 12 h is adequate in geographical areas where there is no quinine resistance—i.e., in Africa (WALLER *et al.*, 1990, 1995; WINSTANLEY *et al.*, 1993). In areas of more resistance, quinine should be given at 8 h intervals. Some physicians prefer to use a continuous infusion, and prepare the day's quinine in a single graduated infusion bag or bottle. For small children, the safest administration method is by microdrop chamber or infusion pump if available. If there is no improvement in the clinical condition of the patient, or acute renal failure develops, the dose of quinine should be reduced by one-third on the third day of treatment (for example, 10 mg/kg every 8 h should be reduced to 7 mg/kg every 8 h after 48 h of treatment). All patients receiving parenteral quinine, especially pregnant women, are at risk of developing quinine-induced hyperinsulinaemic hypoglycaemia (WHITE *et al.*, 1983a; LOOAREESUWAN *et al.*, 1985a; KRISHNA *et al.*, 1994a). In children this can usually be prevented by continuous infusion of 5–7·5% dextrose (TAYLOR *et al.*, 1988), but the possibility of hypoglycaemia should be considered, especially in patients requiring parenteral treatment for more than 48 h, or in those being given intramuscular quinine, and not receiving intravenous fluids. Adult patients who become hypoglycaemic may need a maintenance infusion of 10% dextrose after correction of the blood glucose to prevent further hypoglycaemia (DAVIS *et al.*, 1993a, 1993b), but even this will not prevent recurrences in every case and the blood glucose must be checked repeatedly. Severe quinine toxicity (blindness, deafness, hypotension, cardiac dysrhythmias) is rare in the treatment of severe malaria (PUKRITTAYAKAMEE *et al.*, 1994; WHITE, 1995; BETHELL *et al.*, 1996). In suspected quinine poisoning, by oral or parenteral routes, elimination of quinine may be accelerated by oral or nasogastric administration of activated charcoal (PRESCOTT *et al.*, 1989).

Quinine can be administered by deep intramuscular injection if intravenous infusion is not possible (CHONGSUPHAJAISIDDHI *et al.*, 1983; SHANN *et al.*, 1985; WATTANAGOON *et al.*, 1986; MANSOR *et al.*, 1990; WALLER *et al.*, 1990; PASVOL *et al.*, 1991). The dose regimen is the same as that given intravenously. More dilute solutions (e.g., 60 mg/mL) are less painful than the undiluted fluid (300 mg/mL) and less likely to cause sterile abscess or muscle necrosis. In Viet Nam, tetanus following intramuscular quinine administration is almost invariably fatal (YEN *et al.*, 1994). Sciatic nerve damage may occur and so it is essential that a scrupulously aseptic technique is employed and the injections are given into the anterior thigh, not the buttock. Another important reason for avoiding intragluteal injections is that absorption from this site is slow and uncertain. Provided that these measures are followed, intramuscular quinine is well tolerated (TRAN *et al.*, 1996). It is particularly important to prevent and recognize quinine-induced hypoglycaemia in patients, especially children, receiving intramuscular quinine, since they may not have an intravenous infusion in place for infusion of glucose. Blood glucose levels must be monitored frequently.

At least 3 doses of parenteral quinine should be given but oral antimalarial treatment should be substituted as soon as possible thereafter. In some areas sulphadoxine/pyrimethamine is an alternative to oral quinine. In areas of multidrug resistance, the addition of a 7 d course of doxycycline 3 mg/kg/d or tetracycline (4 mg/kg 4 times daily) to quinine will reduce the incidence of recrudescence but this should not be started until the patient can take oral medication and, in the case of tetracycline, renal function is normal. Tetracycline should not be given to pregnant women, or to children aged <8 years. In pregnant women or children less than 8 years old, clindamycin, 10 mg/kg twice daily, should be given for one week. In Viet Nam mefloquine was associated with unacceptable incidence of serious neuropsychiatric reactions if given immediately following severe malaria (MAI *et al.*, 1996), but this has not been the experience in Thailand, where the incidence of such reactions may be lower (S. Looareesuwan, personal communication).

Some preliminary studies of intrarectal quinine gluconate or Quinimax® (a water-soluble combination of cinchona alkaloids) have yielded encouraging results, suggesting that this route of administration might be practicable and effective when quinine cannot be given by intravenous infusion or intramuscular injection (BARENNES *et al.*, 1995, 1996a, 1996b).

Quinidine

In situations where quinine is not available but quinidine is, the latter drug may be used although there is some controversy over the correct dosage regimens (KAIN *et al.*, 1996; WHITE & WARRELL, 1996). In comparison with the treatment of severe falciparum malaria with quinine, for which there is extensive information, there are few data on which to base treatment recommendations for quinidine. The properties of the 2 drugs are similar but their pharmacokinetics are different.

Quinidine's distribution volumes and systemic clearance are greater, plasma protein binding is less, and blood concentrations for the same dose are approximately 30–50% lower. Quinidine is both more toxic and more active as an antimalarial drug. Parenteral quinidine is available as both hydrochloride and gluconate salts, and therefore recommendations given here as doses of **base**. The therapeutic range for the anti-arrhythmic activity of quinidine at steady state has been estimated at between 3 and 8 mg/L when measured by the extraction–fluorescence method (which also measures the bioactive metabolites) and approximately 2 to 5 mg/L when measured by specific high-performance liquid chromatography (HPLC). The therapeutic range for antimalarial treatment with quinidine is not known precisely, but considering the experience in cardiovascular disease, and its 2–3-fold greater activity in vitro compared with quinine, it has been suggested that total plasma concentrations between 4 and 8 mg/L should represent a reasonable compromise between efficacy and toxicity (compared to 8–20 mg/L for quinine, which corresponds to a free concentration of 1–2 mg/L).

The dose recommendations for quinidine in severe malaria area based on 2 studies. In 14 adults Thai patients with severe falciparum malaria, intravenous quinidine gluconate was given at a dose of 15 mg base/kg over 4 h followed by 7·5 mg base/kg every 8 h until oral treatment could be substituted (i.e., 52·5 mg/kg in 48 h) (PHILLIPS *et al.*, 1985). Mean total plasma quinidine concentrations, measured by the extraction–fluorescence method, were 9·2 mg/L (standard deviation [SD]=2·7) with a range of 4·4 to 14·3 mg/L at the end of the initial loading dose infusion. Post-infusion plasma concentrations generally declined thereafter, reflecting increased clearance and expansion of the apparent volume of distribution with recovery. A similar pattern over nearly two-fold higher plasma concentration range was observed for quinine treatment. In the USA, intravenous quinidine was given at a dose of 6·2 mg **base**/kg infused over 1–2 h followed by 0·75 mg base/kg/h by constant infusion (i.e., 22·5% lower than the dose in the Thai study) (MILLER, K. D. *et al.*, 1989a). Five patients with acute falciparum malaria (4 adults and 1 child) and >5% parasitaemia received this infusion alone, and 10 (8 adults and 2 children) received this together with exchange transfusion (MILLER, K. D. *et al.*, 1989a). Compared with the Thailand study, plasma concentrations of quinidine, measured by specific HPLC, were lower (although precise details were not given). Only 2 patients had concentrations exceeding 7 mg/L, whereas in the Thai study all patients' plasma concentrations exceeded 5·8 mg/L after the initial infusion. This concentration was considered to correspond to the minimum inhibitory concentration (MIC) for *P. falciparum* isolates from Thailand at the time. Exchange transfusion would be expected to result in an increased free fraction of quinidine because of the normal α-1 acid glycoprotein levels in the exchanged blood, and this would change the relationship between total plasma quinidine levels and toxicity. These 2 studies were sufficient to justify the use of quinidine as an alternative to quinine in North America, as quinidine was widely available whereas quinine was not, but both studies were relatively small and cannot be considered definitive. Plasma quinidine levels vary considerably between individuals (three-fold in the Thailand study), and the individual concentration–effect relationships are not predictable. In order to avoid cardiotoxicity, patients with severe falciparum malaria receiving quinidine require careful monitoring. Reversible hypotension and significant QT prolongation are relatively common (whereas they are rare with quinine treatment). Frequent monitoring of blood pressure and continuous electrocardiographic (ECG) monitoring is necessary to avoid cardiotoxicity. An initial dose of 10 mg base/kg should be given over 2 h followed by constant infusion of 0·02 mg base/kg/min. Some authorities recommend the lower dose regimen of 6·25 mg base/kg followed by 0·0125 mg base/kg/min. The debate has centred on the relative risks of toxicity with the higher dose regimen versus the risks of undertreatment with the lower dosage. During administration of intravenous quinidine, if the QRS interval widens by ≥50%, the QT interval exceeds 0·60 s, or the QTc interval is prolonged by more than 25% of the baseline value, the infusion should be stopped until the QT interval prolongation falls below this value. The risk of hypoglycaemia with quinidine is similar to that with quinine.

Artemisinin derivatives are not cardiotoxic and would be an appropriate alternative treatment. As with quinine, quinidine doses should be reduced by one-third to one-half on the third day of treatment if there is no improvement in overall condition, or if acute renal failure develops. Oral treatment with quinine (or quinidine if no alternative is available) should be substituted as soon as possible to complete 7 d of treatment.

Artemisinin derivatives

Parenteral treatment. The most important question in antimalarial drug treatment of severe malaria is whether the artemisinin derivatives can reduce mortality better than quinine. Four recently published randomized controlled trials have compared parenteral quinine and intramuscular artemether (TRAN *et al.*, 1996; BOELE VAN HENSBROEK *et al.*, 1996a; MURPHY *et al.*, 1996; TAYLOR *et al.*, 1998) and none has shown a clear and unequivocal benefit for either drug in outcome measures as either mortality or incidence of residual neurological sequelae. Although artemether accelerated parasite clearance consistently, fever clearance was faster in only one study and either similar or slower than that following quinine in the other studies. In the 2 largest trials, a double-'blind' comparison of intramuscular quinine and artemether in Vietnamese adults (TRAN *et al.*, 1996), and an open randomized comparison of intravenous quinine and intramuscular artemether in Gambian children (BOELE VAN HENSBROEK *et al.*, 1996a), which together enrolled over 1000 patients, artemether was associated with delayed recovery from coma. This unexpected finding in 2 very large series has not been explained satisfactorily. It could have resulted from a neurotoxic effect (although there was no other evidence at all of neurotoxicity), or a beneficial effect of artemether in saving the most seriously ill patients whose recovery was then protracted, or it could possibly be a chance finding. The true benefits of artemether, if any, are likely to be revealed by a planned meta-analysis of all these studies. Several lines of evidence suggest that intramuscular artemether (or arteether, which is still under development) may not be the best formulation for severe malaria. These are oil-based formulations and may be inadequately or erratically absorbed in severely ill patients (MURPHY *et al.*, 1997). This would offset any intrinsic advantage in rapid parasite killing. Furthermore, these formulations are more neurotoxic in animals models than the water-soluble derivatives and the oil-based formulations when given orally (although there is no evidence of neurotoxicity in man).

There are fewer data on the use of artesunate in severe malaria, although it is more widely used than artemether in many countries. Although theoretically preferable, as the drug can be given intravenously and is rapidly absorbed after intramuscular administration (HIEN *et al.*, 1992), there has been no large comparative trial to indicate whether artesunate is superior to artemether or quinine. There is no currently available parenteral formulation of artesunate produced to good manufacturing practices standards.

Both artemether and artesunate may be given once daily, although many physicians prefer to administer a second dose of artesunate 4–12 h after the first. The drugs are very well tolerated and cause no local reac-

tion. Artemether is usually dispensed in 1 mL ampoules containing 80 mg of artemether in peanut oil. Artesunate is dispensed as a vial of dry artesunic acid powder which is unstable in solution at neutral pH, and is dissolved in 0·6 mL of 5% sodium bicarbonate before being drawn into a small volume of 5% dextrose (usually 3–5 mL) before intravenous 'push' (bolus) or intramuscular injection.

Suppositories. Artemisinin and its derivatives may be administered by the rectal route. Suppository formulations of artemisinin, developed originally in China, have proved highly effective in clinical tests in adults and children with severe malaria in Viet Nam. The therapeutic response has been as rapid as that following parenteral administration of artesunate or artemether, and the suppositories have been very well tolerated (CAO *et al.*, 1997; HA *et al.*, 1997). Studies are now in progress evaluating a suppository formulation of artesunate (LOOAREESUWAN *et al.*, 1995a, 1997; HALPAAP *et al.*, 1998; SABCHAREON *et al.*, 1998) and intrarectal administration of the parenteral formulation of artemether. Plasma concentration profiles are more erratic following administration by suppository compared to the intravenous route, but inadequate absorption is unusual. Overall, these studies indicate that the rectal route of administration may allow effective antimalarial treatment to be administered to severely ill patients by unskilled health workers at a very peripheral level of health care. The hope is that this will prevent the potentially life-threatening delay in administering effective antimalarial treatment to patients with severe malaria. Studies are in progress to evaluate their impact on malaria morbidity and mortality.

Oral administration. Not all patients with severe malaria are unable to take oral drugs. In general, if an oral antimalarial drug is the only formulation available, and the patient is conscious, this should be given pending transfer to a facility where parenteral administration can be supervised. Patients with hyperparasitaemia, but no sign or symptom of vital organ dysfunction, are at risk of developing severe malaria. Oral artesunate has been shown to be superior to an intravenous quinine loading dose regimen in a series of 60 Karen patients with uncomplicated 'hyperparasitaemia' (>4%) studied on the western border of Thailand (LUXEMBURGER *et al.*, 1995). Oral artesunate is rapidly absorbed and may be particularly useful in patients with high parasitaemias (usually associated with a predominance of young ring-form parasites) because of its earlier stage-specificity compared to quinine (TER KUILE *et al.*, 1993a). Maturation of the large number of circulating parasites to the more pathogenic sequestering stages is thus prevented.

Pharmacokinetics. There are still insufficient data on the pharmacokinetic properties of artemisinin and its derivatives in malaria. In general this group of drugs is well absorbed after oral administration, is erratically absorbed from oil-based formulations given by intramuscular injection or suppositories, and is eliminated rapidly with elimination half-lives of 1–2 h. There are scant data concerning parenteral artesunate, but these also indicate very rapid elimination in severe malaria. Intramuscular artemether absorption varies considerably and there is recent evidence that absorption is impaired particularly in children with acidosis—a group with a poor prognosis which needs the most urgent treatment (MURPHY *et al.*, 1997). Artemisinin is biotransformed in the liver to biologically inactive metabolites, but artesunate and artemether are converted to a more active metabolite, dihydroartemisinin (DHA), which is further transformed to inactive metabolites. DHA contributes nearly all the antimalarial activity following artesunate administration and most of that resulting from oral administration of artemether, but the parent compound predominates after intramuscular artemether injections (TEJA-ISAVADHARM *et al.*, 1996). Plasma protein binding has been studied only in the case of arteether, which appears to be bound largely to the acute phase protein α_1-acid glycoprotein. There is no information on the disposition of these drugs in patients with hepatic dysfunction or renal failure, but in the absence of further data no dose adjustment is recommended.

Toxicity. These compounds are very well tolerated with no attributable local or systemic adverse effect. Although reticulocyte counts may be depressed in the first week of treatment (CAO *et al.*, 1997), there is no increase in the incidence of anaemia and no obvious pathological consequence. Blackwater fever has followed artemether and artesunate treatment (CHAU *et al.*, 1996), with an incidence approximately similar to that following quinine.

In all animal species studied to date (rodents, dogs, monkeys) intramuscular artemether and the closely related compound arteether have produced an unusual selective pattern of damage to certain brain stem nuclei—particularly those involved in the auditory relay. There is no evidence to date of similar damage in humans. Recent studies of auditory-evoked potentials in Vietnamese and Thai patients have provided reassuringly normal data (M. van Vugt *et al.*; Tran Tin Hien & J. Farrar, personal communications). In a series of 3662 patients with uncomplicated malaria who received artemisinin derivatives on the western border of Thailand, there was no evidence of any adverse nervous system effect (PRICE *et al.*, 1999). Despite these reassuring data, this remains an area of concern where more clinical, experimental and pathological data are required. The water-soluble compounds and the oral routes of administration have given significantly less neurotoxicity than intramuscular administration of the oil-based compounds artemether and arteether in experimental animals (NONTPRASERT *et al.*, 1988). Preliminary observations in women who have received artemisinin derivatives in pregnancy suggest no adverse effect either during gestation or on the baby (MCGREADY *et al.*, 1998). There is no reason to date to withhold these drugs from pregnant women with severe malaria.

Sulfadoxine/pyrimethamine (SP)

An intramuscular preparation (i.e., 500 mg sulfadoxine and 25 mg pyrimethamine in a 2·5 mL ampoule) is available, and has been tested in adults and children in Africa, Thailand and Brazil (WOLFENSBERGER, 1971; MEYER, 1972; HARINASUTA *et al.*, 1988; SALAKO *et al.*, 1990).

The dosage recommended by the manufacturer, sulfadoxine 25 mg/kg plus pyrimethamine 1·25 mg/kg as a single dose, has been used in most studies. It has been argued that the narrow stage-specificity, confined to DNA synthesis in the late-stage trophozoite, would make the combination less effective in the treatment of severe disease. This has not been established.

Comparative studies with oral formulations have not shown that sulfadoxine/pyrimethamine acts more slowly than chloroquine, quinine or mefloquine (NEVILL & WATKINS, 1990; WATT & SHANKS, 1991), while in trials with intramuscular formulations, sulfadoxine/pyrimethamine has reduced parasitaemia more rapidly than chloroquine (in the face of resistance to the latter) (SALAKO *et al.*, 1990) and as rapidly as quinine (SIMÃO *et al.*, 1991), though more slowly than artemether (SALAKO *et al.*, 1994). In a limited series of pregnant women in the second and third trimesters, the combination, given intramuscularly, was safe and effective (SOWUNMI *et al.*, 1993) (see also pp. S1/65–S1/66). There are few pharmacokinetic data on intramuscular sulfadoxine/pyrimethamine, but recent studies in children with severe malaria and children with uncomplicated falciparum malaria but with high parasitaemia indicated that plasma concentrations of sulfadoxine were relatively low, while pyrimethamine concentrations were relatively higher than in healthy subjects

(WINSTANLEY *et al.*, 1992; NEWTON *et al.*, 1993), although both were still in the putative therapeutic range from one until 72 h after injection.

Adding sulfadoxine/pyrimethamine to quinine at the start of treatment does not reduce the parasite clearance time (NEWTON *et al.*, 1993). The combination of sulfadoxine/pyrimethamine with artemisinin is antagonistic in *P. berghei* rodent malaria (CHAWIRA *et al.*, 1987), and one clinical study found rather poor efficacy of the triple combination of artemether, sulfadoxine and pyrimethamine (NAING *et al.*, 1988).

Intramuscular sulfadoxine/pyrimethamine can be effective in a single dose, and severe reactions to the formulation have not been reported. However, there is little information on its efficacy and pharmacokinetics in patients with life-threatening malaria. Furthermore, in many areas, effectiveness will probably become increasingly compromised by resistance. For severe malaria, it should therefore be used only when effective alternatives are not available, or cannot be given safely, or where the single dose presents a critical advantage.

The intramuscular preparation is very viscous but is not painful to recipients. For patients used to the rapid symptomatic improvement following chloroquine treatment, attributable to its anti-inflammatory effect, sulfadoxine/pyrimethamine treatment may seem disappointingly slow, but this should not discourage the clinician.

Chloroquine

The role of chloroquine in severe malaria has declined with the inexorable advance of chloroquine resistance. Chloroquine is still widely used, and there is evidence to suggest that in fully sensitive malaria it is superior to quinine (WILSON & EDESON, 1958; WHITE *et al.*, 1989), but it can be considered the drug of choice only in those few areas without chloroquine resistance (Central America north of the Panama canal, Haiti, Dominican Republic, Argentina, some parts of North Africa and the Middle East, and some other localized areas). If in doubt quinine should be used. Chloroquine is formulated as phosphate, hydrochloride or sulphate salts. These are stable for long periods at room temperature. There appears to be no difference between these salts, but to avoid confusion chloroquine is prescribed in doses of **base**. High blood concentrations of chloroquine resulting from rapid intravenous, intramuscular or subcutaneous administration may be hypotensive and negatively inotropic (LOOAREESUWAN *et al.*, 1986). Intravenous chloroquine must therefore be given by slow rate-controlled intravenous infusion, and never by intravenous injection. Continuous infusion of the entire 25 mg **base**/kg dose over 30 h (5 mg **base**/kg every 6 h) is safe and effective, although infusion of 10 mg **base**/kg over 8 h followed by 15 mg **base**/kg every 8 h over 24 h would provide a theoretically preferable profile (this is very similar to the oral dose regimen) (WHITE *et al.*, 1988b).

If intravenous infusion is not possible, chloroquine may be given by subcutaneous or intramuscular injection. The drug is very rapidly absorbed (WHITE *et al.*, 1987b), even in severely ill patients, and so small frequent doses are necessary to avoid transient cardiovascular toxicity. In a study of 16 Gambian children with malaria requiring parenteral treatment, intramuscular or subcutaneous chloroquine in a dose of 3·5 mg **base**/kg every 6 h was safe and effective (WHITE *et al.*,

Table 8. Severe falciparum malaria: antimalarial chemotherapy in adults and children at facilities able to provide only minimal health care[a] (periphery/community)[b]

Chloroquine-resistant, or sensitivity unknown	Chloroquine-sensitive
1. *Suppositories of artemisinin*:[c] 40 mg/kg loading dose as suppositories intrarectally, followed by 20 mg/kg at 4, 24, 48 and 72 h followed by an oral antimalarial drug. *Suppositories of artesunate*:[c] One 200 mg suppository intrarectally at 0, 4, 8, 12, 24, 36, 48 and 60 h followed by an oral antimalarial drug.[d]	1. *Chloroquine*: 10 mg **base**/kg of body weight as tablets/syrup by mouth or nasogastric tube, *then* refer the patient to a higher level of health care for parenteral treatment OR continue 5 mg **base**/kg at 5, 24 and 48 h later
OR	**OR**
2. *Quinine*: tablets by mouth 10 mg quinine **salt**/kg, *then* refer the patient to a higher level of care for parenteral treatment OR continue 10 mg quinine **salt**/kg (maximum 600 mg) 8 hourly to complete 7 d treatment[e,f]	2. *Suppositories of artemisinin or artesunate, oral quinine, mefloquine or sulfadoxine/pyrimethamine* (see left-hand column)
OR	
3. *Mefloquine*: tablets by mouth, 15 mg **base**/kg single dose. If immediate referral is not possible in areas of suspected or proven mefloquine resistance, a further 10 mg **base**/kg should be given on the following day.[f]	
OR	
4. *Sulfadoxine–pyrimethamine*[g] tablets by mouth, sulfadoxine 25 mg/kg pyrimethamine 1·25 mg/kg single dose (maximum 1500 mg sulfadoxine/75 mg pyrimethamine).	

[a]For definition see text, p. S1/55.
[b]Patients with severe falciparum malaria should be treated at the highest available level of health care. However, even if referral is possible, they must be treated immediately as described in this Table, and then transferred.
[c]Artemisinin and artesunate suppositories are registered for use in some countries only, and experience with them is limited. If suppository formulations are not available, tablets of artemisinin derivatives should be given orally if possible, or crushed and given by nasogastric tube.
[d]In Viet Nam 4 mg/kg of artesunate in suppository form (China) intrarectally as a loading dose, followed by 2 mg/kg at 4, 12, 48 and 72 h, followed by an oral antimalarial drug, was as effective as artemisinin suppositories (Tran Tinh Hien, personal communication).
[e]In areas where a 7 d course of quinine is not curative (e.g., Thailand) add a course of **oral** tetracycline 4 mg/kg 4 times daily or doxycycline 3 mg/kg once daily except for children under 8 years of age and pregnant women, or clindamycin 10 mg/kg twice daily for 3–7 d.
[f]In patients who cannot swallow, nasogastric tubes may be used by properly trained health workers to administer crushed tablets.
[g]Sulfadoxine/pyrimethamine should be given only in areas where there is known to be full sensitivity.

1988b). However, subcutaneous chloroquine was the least effective of 3 regimens tested in children with impaired consciousness in Ibadan, where 10% of infections are resistant to chloroquine at the RI level (L. Salako, personal communication). In The Gambia, most of the children required 2 parenteral doses before changing to oral chloroquine; in the remainder, peak blood chloroquine concentrations after the third and subsequent doses ranged from 560 to 2500 ng/mL (WHITE *et al.*, 1988b). WHITE *et al.* (1987b) predicted that chloroquine in a dose of 2·5 mg/kg every 4 h by intramuscular or subcutaneous injection would be an acceptable alternative to the six-hourly regimen. Oral therapy should be substituted as soon as possible. The usual total treatment dose is 25 mg **base**/kg. Larger total doses have been suggested in areas with low-grade resistance but there is no evidence of improved efficacy. If parenteral administration is not possible, oral or nasogastric chloroquine should be given pending transfer to hospital or clinic. Chloroquine dose regimens are unchanged in children, in pregnancy, or in patients with liver or renal dysfunction. Many patients will have received some previous treatment but this should not alter the treatment regimen, unless chloroquine has been administered in the preceding 4 h. Chloroquine suppositories may be an alternative for the treatment of severe chloroquine-sensitive malaria when injections cannot be given, but these are not generally available and have not been subjected to adequate clinical trials (WESTMAN *et al.*, 1994; ANTI-ABONG *et al.*, 1995).

Antimalarial chemotherapy at different levels of health service is summarized in Tables 8–10.

Mefloquine

There is no parenteral formulation of mefloquine, and therefore this drug should not be used as the sole treatment for severe malaria. Nasogastric mefloquine suspension was rapidly, but probably incompletely, absorbed in patients with cerebral malaria (CHANTHAVANICH *et al.*, 1985; KARBWANG & WHITE, 1990). This route cannot be relied upon in seriously ill patients.

Amodiaquine

Amodiaquine is a Mannich base 4-aminoquinoline used widely in the past to treat and prevent malaria. Its use was substantially reduced after reports in the mid 1980s of fatal adverse drug reactions in travellers using amodiaquine as prophylaxis. So far, such adverse reactions have been described only during prophylaxis. Based on reported rates, the risk of serious adverse reactions associated with prophylactic use of amodiaquine can be estimated to be approximately 1:2100 treatments for agranulocytosis, 1:15 000 for hepatotoxicity, and 1:30 000 for aplastic anaemia, with a total case fatality rate of 1:15 650. The risk of fatal reactions to amodiaquine is of the same order of magnitude as that to sulfadoxine/pyrimethamine (PHILLIPS-HOWARD & WEST, 1990).

Amodiaquine treatment appears to be safer than amodiaquine prophylaxis. A systematic review of published and unpublished data showed that amodiaquine appeared to be no more toxic than chloroquine or sulphadoxine/pyrimethamine when administered at total doses up to 35 mg/kg over 3 d for treating adult and children with uncomplicated falciparum malaria (OLLIARO *et al.*, 1996; WHITE, 1996b). In that review, which was essentially based on African data, amodiaquine was significantly more effective than chloroquine in clearing parasites in all analyses done, with a tendency also for faster clinical recovery; compared to sulphadoxine/pyrimethamine, no difference in parasitological outcomes was observed within 7 d of study, while sulfadoxine/pyrimethamine was superior during longer-term follow-up and faster symptomatic amelioration was achieved with amodiaquine.

Table 9. Severe falciparum malaria: antimalarial chemotherapy in adults and children at facilities able to provide intermediate health care[a]

Chloroquine-resistant, or sensitivity unknown	Chloroquine-sensitive
1. *Quinine*: 20 mg dihydrochloride **salt**/kg (loading dose)[b,f] diluted to 60 mg/mL given intramuscularly (divided sites[c]), then 8 hours after the start of the loading dose give 10 mg/kg[d] 8 hourly until the patient can swallow, then quinine tablets approximately 10 mg **salt**/kg (maximum 600 mg) 8–12 hourly to complete 7 days' treatment[e] or, if there is well documented full sensitivity, give a single dose of 25 mg/kg sulfadoxine and 1·25 mg/kg pyrimethamine (maximum 1500 mg sulfadoxine/75 mg pyrimethamine).	1. *Chloroquine*: 3·5 mg **base**/kg every 6 h given intramuscularly[c] or subcutaneously. Change to oral treatment as soon as the patient can swallow tablets to complete a total dose of 25 mg **base**/kg.
OR	**OR**
2. *Artesunate* [f,g]: 2·4 mg/kg intramuscularly[c] followed by 1·2 mg/kg at 12 and 24 h, then 1·2 mg/kg daily for 6 d.	2. *Quinine, artesunate, artemether or sulfadoxine/pyrimethamine*[h] (see left-hand column).
OR	
3. *Artemether* [f]: 3·2 mg/kg intramuscularly[c] on the first day, followed by 1·6 mg/kg daily for a minimum of 3 d until the patient can take oral treatment or another effective antimalarial. In children the use of a 1 mL tuberculin syringe is advisable since the injection volumes will be small.	

[a]For definition see text, pp. S1/55–S1/56.
[b]Loading dose should not be used if the patient has received quinine, quinidine or mefloquine within the preceding 12 h.
[c]Intramuscular injections should be given with maximal sterile precautions into the anterior thigh, **not the buttock**.
[d]If there is no clinical improvement after 48 h of parenteral therapy, reduce the quinine maintenance dose to 5–7 mg/kg body weight.
[e]In areas where a 7 d course of quinine is not curative (e.g., Thailand) add a course of **oral** tetracycline 4 mg/kg 4 times daily or doxycycline 3 mg/kg once daily except for children under 8 years of age and pregnant women, or clindamycin 10 mg/kg twice daily for 3–7 d.
[f]If parenteral formulations are not available consider suppository formulations or giving crushed tablets by nasogastric tube.
[g]Artesunate was developed primarily for intravenous injections. The data on its intramuscular use are limited.
[h]If neither quinine nor artemisinin derivatives are available then, in areas with documented sensitivity, sulfadoxine–pyrimethamine may be given as a single intramuscular injection in divided sites. For adults 3×2·5 mL ampoules may be given and for children 4 years and older, half of one 2·5 mL ampoule (one ampoule contains 500 mg sulfadoxine and 25 mg pyrimethamine).

Table 10. Severe falciparum malaria: antimalarial chemotherapy in adults and children at facilities able to provide maximal possible health care[a]

Chloroquine-resistant, or sensitivity unknown	Chloroquine-sensitive
1. *Quinine*: Adults—20 mg dihydrocyhloride **salt**/kg (loading dose)[b,c] diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 h then, 8 h after the start of the loading dose, 10 mg/kg[d] over 4 h every 8 h until the patient can swallow, then quinine tablets approximately 10 mg quinine **salt**/kg (maximum 600 mg) every 8–12 h to complete 7 d treatment[e] OR give a single dose of 25 mg/kg sulfadoxine and 1·25 mg/kg pyrimethamine (maximum 1500 mg sulfadoxine/75 mg pyrimethamine). Children—20 mg dihydrochloride **salt**/kg (loading dose)[b,c] diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 h then, 12 h after the start of the loading dose, give 10 mg **salt**/kg[d] over 2 h every 12 h until the patient can swallow, then quinine tablets approximately 10 mg **salt**/kg every 8 h to complete 7 d treatment[e] OR give a single dose of 25 mg/kg sulfadoxine and 1·25 mg/kg pyrimethamine.	1. *Chloroquine*: 10 mg **base**/kg in isotonic fluid by constant rate intravenous infusion over 8 h, followed by 15 mg/kg over 24 h.
OR	**OR**
2. *Artesunate*[f]: 2·4 mg/kg intravenously on the first day followed by 1·2 mg/kg daily for a minimum of 3 d until the patient can take oral therapy or another effective antimalarial.	2. *Chloroquine*: 5 mg **base**/kg in isotonic fluid by constant rate intravenous infusion over 6 h, every 6 h, to a total dose of 25 mg base/kg over 30 h.
OR	**OR**
3. *Artemether*: 3·2 mg/kg intramuscularly on the first day, followed by 1·6 mg/kg daily for a minimum of 3 d until the patient can take oral treatment or another effective antimalarial. In children the use of a 1 mL tuberculin syringe is advisable since the injection volumes will be small.	3. *Quinine, artesunate, artemether or quinidine* (see left-hand column)
OR	
4. *Quinidine*: 15 mg **base**/kg (loading dose)[b] by intravenous infusion over 4 h then, 8 h after the start of the loading dose, give 7·5 mg **base**/kg[d] over 4 h every 8 h until the patient can swallow, then quinine tablets to complete 7 d treatment[e] OR give a single dose of 25 mg/kg sulfadoxine and 1·25 mg/kg pyrimethamine.	

[a]For definition see text, p. S1/56.
[b]Loading dose should not be used if the patient received quinine, quinidine or mefloquine within the preceding 12 h.
[c]Alternatively the loading dose can be administered as 7 mg **salt**/kg by intravenous infusion (or pump) over 30 min followed immediately by 10 mg/kg diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 h.
[d]If there is no clinical improvement after 48 hours of parenteral therapy, reduce the maintenance dose to 5–7 mg quinine dihydrochloride/kg or to 3·75–5 mg quinidine **base**/kg every 8 h.
[e]In areas where a 7 d course of quinine is not curative (e.g., Thailand) add a course of **oral** tetracycline 4 mg/kg 4 times daily or doxycycline 3 mg/kg once daily except for children under 8 years of age and pregnant women, or clindamycin 10 mg/kg twice daily for 3–7 d.
[f]Artesunic acid 60 mg is dissolved in 0·6 mL of 5% sodium bicarbonate diluted to 3–5 mL with 5% (w/v) dextrose and given immediately by intravenous ('push') bolus injection.

Amodiaquine is widely available in malaria endemic countries, particularly francophone Africa, as the chlorhydrate in either tablet form (200 and 600 mg) or suspension (50 mg per 5 mL).

Amopyroquine

Amopyroquine is also a Mannich base. Although it has theoretical advantages over the closely related amodiaquine (its activity is due to the parent compound; VERDIER *et al.*, 1989), it is more active *in vitro* against chloroquine-resistant strains of *P. falciparum*, although partial cross-resistance exists between chloroquine and amopyroquine (BASCO & LEBRAS, 1993). The major disadvantage of amopyroquine is that it undergoes extensive first-pass metabolism after oral administration, so that it can be administered only intramuscularly. The drug is not effective in a single injection and a total dose of 12 mg/kg over 2 d is required to achieve cure rates above 90% in Africa (GAUDEBOUT *et al.*, 1993).

At present, the drug is not available for use although it was marketed for a short period in the early 1960s as Propoquine™.

Supportive and ancillary treatments

A number of ancillary treatments has been suggested for cerebral and other forms of severe malaria (WARRELL, 1999). These treatments are reviewed below.

Recommended treatments

Antipyretics. In uncomplicated falciparum malaria, paracetamol has been shown rapidly to lower temperature and improve symptoms associated with fever (KRISHNA *et al.*, 1995a). In a further randomized double-'blind' trial, a single dose of ibuprofen (10 mg/kg) lowered temperatures more than a single dose of paracetamol (15 mg/kg) during the first 4·5 h after treatment (KRISHNA *et al.*, 1995b). However, paracetamol may be safer than ibuprofen, especially in patients

with severe falciparum malaria who have a bleeding diathesis. In Gabonese children, paracetamol was no more effective than fanning and tepid sponging in reducing fever but prolonged *P. falciparum* parasitaemia by a mean of 16 h (BRANDTS *et al.*, 1997).

Anticonvulsants. In Thailand, a double-'blind' placebo-controlled trial of a very small single dose of sodium phenobarbital (200 mg for adults, or 3·5 mg/kg in children), given by intramuscular injection on admission, demonstrated a significant reduction in the incidence of generalized convulsions (WHITE *et al.*, 1988a) but the numbers were insufficient to test the effect on mortality. In a randomized placebo-controlled trial of pheobarbitone prophylaxis (20 mg/kg intramuscularly) in 329 Kenyan children with cerebral malaria, the incidence of convulsions was reduced, but case fatality was significantly increased in the phenobarbitone-treated group (J. Crawley, personal communication). The outcome of this large trial suggests that high dose phenobarbitone anti-convulsant prophylaxis should not be used in severe malaria. It is not known whether lower doses, or other anti-convulsants (e.g., fosphenytoin) would be harmful. No clear recommendation can be given at this time.

Exchange blood transfusion (EBT) in hyperparasitaemia

Patients with high malarial parasitaemia are at increased risk of developing all the severe manifestations of falciparum malaria. The risk is roughly proportional to the parasitaemia (FIELD & NIVEN, 1937; FIELD, 1949) and it has therefore been suggested that exchange blood transfusion might benefit some patients with very high parasite counts. The rationale for exchange transfusion is as follows.

- To remove infected red blood cells from the circulation and therefore to lower parasite burden more rapidly than is possible with chemotherapy alone.
- To reduce rapidly both antigen load and the burden of parasite-derived toxins and metabolites and the host's response to these molecules.
- To replenish healthy and unparasitized red cells with normal mechanical properties and to correct anaemia.

Although carried out on many occasions since 1974 with some encouraging results, there seems to be little consensus about the benefits, dangers and indications for exchange blood transfusion, or guidance on the practical details such as the volume to be exchanged for a given parasitaemia. Mathematical models which relate volume of exchange to reduction in parasitaemia have been assessed (VAN DEN ENDE *et al.*, 1994; WILKINSON *et al.*, 1994). In applying such a model to 17 cases, WILKINSON *et al.* (1994) found that 50% clearance of parasitaemia occurred after less than 70% of the circulating volume had been exchanged. They attributed this to the concurrent antimalarial chemotherapy. Quinine can be expected to reduce the parasite burden by 50% in about 24 h when the parasite is sensitive, while artemisinin derivatives act about twice as fast (HIEN & WHITE, 1993). In highly endemic areas, children with hyperparasitaemia (as high as 80%) can be successfully treated using chemotherapy alone (MORDMÜLLER & KREMSNER, 1998). Non-immune patients with hyperparasitaemia have also been cured without the use of exchange transfusion (MARIK, 1989 [and erratum, 1990]; BURCHARD *et al.*, 1997). There have been a few attempts to compare the results of treatment with exchange blood transfusion with appropriate controls (LOOAREESUWAN *et al.*, 1990; BURCHARD *et al.*, 1997; PINANONG, 1997; HOONTRAKOON & SUPUTTAMONGKOL, 1998). No powerful and adequately designed randomized controlled trial has been carried out and it seems increasingly unlikely that this will ever happen. Recent studies suggest that the benefit from exchange transfusion results from replacing the rigid, non-deformable, unparasitized red cells and not from an effect on parasitaemia (DONDORP *et al.*, 1997).

Exchange blood transfusion should be considered only when adequately screened, pathogen-free, fully cross-matched blood together with high-dependency facilities and trained staff are available. The risks of fluid overload, transfusion reactions, transfusion-related infections and line sepsis must be weighed against the potential benefits of the procedure. These benefits increase as the parasite burden increases, and are most obvious in non-immune patients who have not responded to optimal chemotherapy.

It has been argued that exchange blood transfusion might be of benefit in non-immune patients with over 30% of their erythrocytes infected with *P. falciparum* even in the absence of clinical complications because of the high mortality in such cases despite chemotherapy (WILKINSON *et al.*, 1994). Exchange blood transfusion has also been recommended if more than 10% of the red blood cells are parasitized and there are clinical complications including severe anaemia (haemoglobin <6·0 g/dL) (LOOAREESUWAN *et al.*, 1990; WILKINSON *et al.*, 1994). Some suggested indications for exchange transfusions are given in Table 11.

Table 11. Indications for exchange blood transfusion for hyperparasitaemia in a presumed non-immune patient with *P. falciparum* malaria[a]

Parasitaemia >30% in the absence of clinical complications
Parasitaemia >10% in the presence of severe disease, especially cerebral malaria, acute renal failure, adult respiratory distress syndrome, jaundice and severe anaemia
Parasitaemia >10% and failure to respond to optimal chemotherapy after 12–24 h
Parasitaemia >10% and poor prognostic factors (e.g., elderly patient, late-stage parasites [schizonts] in the peripheral blood)

[a]**Caution**. Exchange blood transfusion should be contemplated only if there is
(i) pathogen-free compatible blood available;
(ii) facilities for safe exchange and adequate clinical monitoring.

*Treatments which are **not** recommended*

A number of ancillary treatments that have been suggested by various authorities which are **not** now recommended are critically reviewed below (Table 12).

Dexamethasone and other corticosteroids. Glucocorticoids were recommended both for their anti-inflammatory effect and their activity in reducing certain types of cerebral oedema. Dexamethasone in an initial dose of 0·5 mg/kg followed by 10 mg every 6 h for 48 h by slow intravenous injection was tested in a double-'blind' pla-

Table 12. Cerebral malaria; experimental ancillary treatments which have *not* yet been proved to be beneficial and which are *not* recommended

Corticosteroids (dexamethasone)	Oxypentifylline (Trental®)
Other anti-inflammatory agents	Hyperbaric oxygen
Other anti-cerebral oedema agents (urea, mannitol, invert sugar)	Cyclosporin A
Low molecular weight dextran	Hyperimmune serum
Adrenaline	Iron chelating agents (desferrioxamine B)
Heparin	Dichloroacetate
Prostacyclin	Anti-tumour necrosis factor antibodies

cebo-controlled trial involving 100 patients with strictly defined cerebral malaria in eastern Thailand (WARRELL *et al.*, 1982). Dexamethasone did not decrease mortality (P=0·8) but significantly prolonged unconsciousness and led to an increased incidence of corticosteroid-related effects including infections and gastrointestinal bleeding. Similar problems have been encountered in patients with septic shock treated with dexamethasone (SPRUNG *et al.*, 1984) and methylprednisolone (BONE *et al.*, 1987), in patients with cerebral haemorrhage treated with dexamethasone (POUNGVARIN *et al.*, 1987), and in patients with respiratory failure treated with methylprednisolone (WEIGELT *et al.*, 1985). STUCK *et al.* (1989) showed, in a meta-analysis, that glucocorticoids increase the risk of lethal and non-lethal infectious complications. The study of cerebral malaria in Thailand was criticized on the grounds that the dose of dexamethasone was much too low (HOFFMAN, 1982) or too high but given for too short a time (REES, 1982, 1983). HOFFMAN *et al.* (1988) carried out a double-'blind' trial of 11·4 mg of dexamethasone/kg over 48 h in 10 stuporose and 28 comatose patients with falciparum malaria in Irian Jaya, Indonesia. The mortality was 12% in each group. Three of the 19 dexamethasone-treated patients, but none of the placebo group, developed gross gastrointestinal bleeding. This study was criticized on the grounds that the patients in the 2 treatment groups were not comparable before treatment and that the numbers were too small to demonstrate a therapeutic effect (COOPER, 1989).

Evidence from clinical studies in humans does not support the hypothesis that cerebral malaria results from an inflammatory breakdown in permeability of the blood–brain barrier resulting in cerebral oedema (LOOAREESUWAN *et al.*, 1983b; WARRELL *et al.*, 1986). The recent evidence that, in African children with cerebral malaria, there is raised intracranial pressure and brain swelling (NEWTON *et al.*, 1991, 1994) suggests a possible therapeutic role for dexamethasone and other corticosteroids (WARRELL, 1999). However, the main cause of these changes in cerebral malaria seems to be an increase in intracranial blood volume, rather than vasogenic cerebral oedema likely to respond to corticosteroid treatment (FISHMAN, 1982). There has been renewed interest in the use of corticosteroids to prevent complications, especially deafness, and to reduce mortality rates in bacterial meningitis.

Corticosteroids are said to control haemolysis in blackwater fever (FLEMING & ALLEN, 1969), but there was no control group in these studies, the patients were not adequately defined (e.g., to exclude G-6PD deficiency), and it is hard to attribute their improvement to corticosteroid alone. CHAROENLARP *et al.* (1979) found no effect of prednisolone on erythrocyte half-life in the acute phase of falciparum malaria. A randomized controlled trial of corticosteroid in Vietnamese patients with fever and haemoglobinuria has been initiated (Tran Tin Hien, personal communication).

Since the place of mega-dose corticosteroid (methylprednisolone 30 mg/kg) in Gram-negative bacterial shock and adult respiratory distress syndrome is still controversial (SPRING *et al.*, 1984; WEIGELT *et al.*, 1985; BONE *et al.*, 1987) and in view of the great expense and special dangers of this treatment in malaria, it cannot yet be recommended. There is no evidence of acute adrenal insufficiency, of the kind envisaged in fulminant meningococcaemia (BRANDTZAEG, 1995), in 'algid' malaria. Plasma cortisol concentrations are not low, and dexamethasone does not correct hypotension.

Corticosteroids should not be used in cerebral malaria; this treatment lacks theoretical basis and clinical evidence and carries a risk of side effects.

Osmotic/diuretic agents for cerebral malaria. Mannitol (COMMEY *et al.*, 1980; COMMEY, 1984) and urea in invert sugar (KINGSTON, 1971) have been used to combat the hypothetical cerebral oedema in cerebral malaria, but the evidence for the benefit is unpublished or unconvincing, and potential dangers include hypo-osmolarity with or without hyponatraemia, hyperkalaemia, and hypervolaemia precipitating pulmonary oedema, oliguria, anuria, hyperazotaemia, and hyperosmolarity with or without hypernatraemia (BONSOM *et al.*, 1970; REIF *et al.*, 1972; NG & SUKI, 1980; WHO, 1980). In Kenyan children with cerebral malaria, NEWTON (1994) monitored intracranial pressure. Mannitol was effective in reducing intracranial pressure, but some children developed intractable intracranial hypertension despite early treatment with mannitol.

Heparin. Heparin has been used in severe malaria in the belief that disseminated intravascular coagulation was important in the pathogenesis of cerebral malaria (JAROONVESAMA, 1972) and pulmonary oedema (PUNYAGUPTA *et al.*, 1974). However, a post-mortem ultrastructural study of patients who died of cerebral malaria found no support for this hypothesis (MACPHERSON *et al.*, 1985). Efficacy of heparin has been claimed (DENNIS *et al.*, 1967; PUNYAGUPTA *et al.*, 1972, 1974; JOHNSON *et al.*, 1977; VON SONNENBURG *et al.*, 1986; RAMPENGAN, 1991), but the danger of heparin in patients with a bleeding diathesis (BOROCHOVITZ *et al.*, 1970) has discouraged any randomized controlled trial of this treatment. The evidence in favour of heparin treatment is unsatisfactory but heparin-induced bleeding is a real danger. **Heparin is therefore contraindicated.**

Dextran. Dextran was suggested to improve blood flow through the small cerebral vessels by reducing blood viscosity (SMITSKAMP & WOLTHIUS, 1971). However, in patients with severe malaria, blood viscosity is already reduced as a result of the severe anaemia. Dextrans occasionally cause severe anaphylactic reactions and, because of their effect on haemostasis (factor VIII), should be used with great caution in patients suffering from bleeding diatheses (LEWIS, 1977).

Prostacyclin. Prostacyclin is a naturally occurring endothelial arachidonic acid derivative which is a potent vasodilator and inhibitor of platelet aggregation. At least one reported case of severe malaria (WESTON *et al.*, 1982) and 2 unreported cases have been treated with prostacyclin, but it is impossible to decide to what extent prostacyclin contributed to their recovery.

Pentoxifylline for cerebral malaria. Pentoxifylline, a methylxanthine, inhibits TNF synthesis by inhibiting phosphodiasterase and increasing intracellular cyclic adenosine monophosphate. In a mouse model of cerebral malaria, pentoxifylline prevented the development of 'cerebral malaria' and reduced TNF bioactivity to undetectable levels (KREMSNER *et al.*, 1991; STOLTENBURG-DIDDINGER *et al.*, 1993). Pentoxifylline has been shown to reduce circulating TNF and IL-6 levels and to produce clinical improvement in patients with severe falciparum malaria (GRANINGER *et al.*, 1991; LANDAU & ATTALI, 1993; DI PERRI *et al.*, 1995) and, in a small randomized controlled trial in children with cerebral malaria in Burundi, pentoxifylline appeared to reduce the duration of coma from a median of 46 h to one of 6 h (DI PERRI *et al.*, 1995). In Thailand, pentoxifylline treatment did not prove effective in adult patients with severe falciparum malaria. (LOOAREESUWAN *et al.*, 1998).

Cyclosporin A. In a mouse model, low dose cyclosporin A prevented 'cerebral malaria' (GRAU *et al.*, 1987a). However, in a double-'blind' randomized controlled trial of cyclosporin A treatment in adults with severe falciparum malaria in Viet Nam, cyclosporin A did not reduce mortality (Trinh Kim Anh, personal communication).

Immunoglobulin. In a squirrel monkey model of falciparum malaria, monoclonal and polyclonal antibodies appeared to reverse cytoadherence of parasitized erythrocytes *in vivo* (DAVID *et al.*, 1983), and human immunoglobulin lowered parasitaemia in patients with

falciparum malaria (McGREGOR *et al.*, 1963). In Malawian children with cerebral malaria, immunoglobulin purified from the plasma of local semi-immune blood donors did not reduce the duration of coma, mortality rate, or the incidence of neurological sequelae (TAYLOR *et al.*, 1992).

Sodium bicarbonate. As in bacterial septicaemia, elevated concentrations of lactate in body fluids indicate severe disease. Hyperlactataemia is a poor prognostic sign. Acidosis in malaria results from many different processes. These include microcirculatory obstruction, increased plasma levels of pro-inflammatory cytokines, hepatic and variable renal dysfunction, and a general increase in glycolysis. There is also anaemia, and sometimes hypoxia, and the predominence of acidosis in malaria (TAYLOR *et al.*, 1993; KRISHNA *et al.*, 1994a; MARSH *et al.*, 1995) has led to specific attempts to reverse it. Sodium bicarbonate is widely used but is generally losing favour as it does not address the underlying pathological process, conveys a considerable sodium load, and may lead to paradoxical worsening of central nervous system acidosis.

Iron chelators. Desferrioxamine B, an iron chelator, has antimalarial activity by withholding iron from the parasites' vital metabolic pathways but it may have a second beneficial effect in severe falciparum malaria by inhibiting iron-induced peroxidant damage to cells and subcellular structures of the brain (GORDEUK *et al.*, 1994).

In Zambian children with cerebral malaria, desferrioxamine treatment produced a significant reduction in the duration of coma from a median of 68·2 h to a median of 24·1 h (GORDEUK *et al.*, 1992). However, comparison with other studies of African children suggests that coma was prolonged in the control group, rather than shortened in the desferrioxamine-treated group.

In a subsequent study which enrolled 352 children with cerebral malaria, desferrioxamine did not significantly affect coma recovery but was associated with increased mortality (P=0·05) (THUMA *et al.*, 1998). **These data suggest that desferrioxamine should not be used in cerebral malaria.** One possible explanation for the discrepancy between these 2 studies was that in the first study no loading dose of quinine was given, whereas it was in the second in which, in contrast to the first study, coma recovery times were similar to those reported elsewhere (VAN DER TORN *et al.*, 1998).

Dichloroacetate in lactic acidosis. Dichloroacetate activates the pyruvate dehydrogenase complex of many tissues by inhibiting the kinase responsible for phosphorylation and inactivation of the complex (CRABB *et al.*, 1981). Dichloroacetate lowers circulating lactate levels in a number of conditions complicated by hyperlactataemia without improving survival (STACPOOLE *et al.*, 1988, 1992). In experimental murine malaria and severe falciparum malaria in humans, dichloroacetate reduces hyperlactataemia (HOLLOWAY *et al.*, 1991; KRISHNA *et al.*, 1994b) but, so far, no effect on survival has been demonstrated, except in rats (HOLLOWAY *et al.*, 1991, 1995).

Anti-TNF antibodies. The association between high circulating TNF levels and bad prognosis in cerebral malaria (KWIATKOWSKI *et al.*, 1990; GRAU *et al.*, 1989b) suggested a role for anti-TNF antibodies in the treatment of cerebral malaria. In Gambian children, a pilot dose-finding study employing a murine monoclonal anti-TNF antibody showed there was a dose-dependent increase in total plasma TNF levels and a dose-dependent reduction in fever. A double-'blind' placebo-controlled trial in 302 children failed to demonstrate any benefit of this treatment on survival; there was an excess of neurological sequelae in the group treated with anti-TNF monoclonal antibody (BOELE VAN HENSBROEK, 1996b). Polyclonal anti-TNF antibodies may prove more effective in neutralizing TNF activity (LOOAREESUWAN *et al.*, 1999).

Adrenaline. Adrenaline was originally used in the 1930s in the belief that it helped to eliminate parasites from the spleen. The benefits of adrenaline were not confirmed by FINDLAY (1950) or by BRUCE-CHWATT (1963, 1982). Intramuscular or subcutaneous injection of adrenaline (1 mL of 0·001% or 0·01% over 5 min) was recommended as a prelude to intravenous quinine therapy by PATRICK (1968, 1982) and this treatment has been suggested in standard textbooks. However, there is no evidence that this potentially dangerous drug is needed or is beneficial in severe malaria (HALL, 1974; WHITE & WARRELL, 1982). Adrenaline produces serious lactic acidosis in both severe falciparum malaria and severe sepsis (DAY *et al.*, 1996). Intravenous adrenaline is particularly dangerous; it can cause fatal cardiac arrhythmias and may cause splenic rupture in patients with splenomegaly.

Taken together, these various studies show no evidence of any benefit for any of the ancillary treatments which have been investigated in severe falciparum malaria.

Management of specific problems in severe falciparum malaria

In patients with suspected or proven severe falciparum malaria, the principles of practical management are as follows.

- Early suspicion of diagnosis, transfer to the highest level of care available or referral. Rapid clinical assessment.
- Early antimalarial chemotherapy using optimal doses of an appropriate agent administered by the parenteral route.
- Prevention, or early detection and treatment, of complications (e.g., convulsions, hypoglycaemia, hyperpyrexia).
- Correction of fluid, electrolyte and acid–base balance.
- Avoidance of harmful ancillary treatments (e.g., corticosteroids).

Severe malaria is a medical emergency and demands urgent clinical assessment and treatment. The sequence of events suggested for the initial management of these patients is shown in the box below.

Initial management of a patient with severe malaria

(i) Clear and maintain the airway.
(ii) Position semi-prone or on side.
(iii) Weigh the patient, calculate dosage.
(iv) Start antimalarial chemotherapy.
(v) Make rapid clinical assessment.
(vi) Exclude or treat hypoglycaemia.
(vii) Assess state of hydration.
(viii) Measure and monitor urine output. If necessary insert urethral catheter.
Measure urine specific gravity.
(ix) Take blood for diagnostic smear, monitoring of blood sugar ('stix' method), haematocrit and other laboratory tests.
(x) Plan first 8 h of intravenous fluids—including diluent for antimalarial drug, glucose therapy and blood transfusion.
(xi) Consider inserting central venous pressure catheter to monitor fluid replacement.
(xii) If rectal temperature exceeds 39°C, remove patient's clothes, use tepid sponge, fan, cooling blanket and consider antipyretic.
(xiii) Lumbar puncture to exclude meningitis or cover with appropriate antibiotic. Consider other infections.
(xiv) Consider need for anticonvulsant and additional drugs (antimicrobials, vitamin K etc.).

Hyperpyrexia

Antipyretics. Antipyretics such as paracetamol, aspirin and non-steroidal anti-inflammatory agents are effective, but the latter 2 carry some risk of causing gastrointestinal bleeding. Powdered paracetamol tablets (dose 15 mg/kg) may be washed down a nasogastric tube, and the drug is sometimes available in the form of suppositories. Quinine and chloroquine have both been reported to have some antpyretic activity, although there is no firm evidence of this. There is no completely satisfactory injectable antipyretic (parenteral formulations of paracetamol contain inadequate doses of the drug). Pyrazolones (e.g., dipyrone 1 g in 2 mL intramuscularly for adults) are effective and widely used in tropical countries, but may cause fatal agranulocytosis.

Other methods of cooling. The efficacy of removing clothing, tepid sponging and fanning has been questioned in children (STEELE *et al.*, 1970; HUNTER, 1973; NEWMAN, 1985). However, in a recent study in Gabonese children with malaria, these methods were as effective as paracetamol in reducing fever (BRANDTS *et al.*, 1997), and in adults they will lower body temperature dramatically, as will the use of a hypothermia blanket.

Cerebral malaria

Patients should be nursed on their side as vomiting is common. They should be turned regularly at intervals of not more than 2 h. A nasogastric tube should be passed and the stomach contents sucked out to reduce the risk of aspiration pneumonia. Eyes should be kept irrigated with saline or artificial tears (acetyl cysteine) and the lids kept closed with eye pads. A urethral catheter should be inserted and urine output recorded accurately. Core (rectal) temperature should be measured frequently or recorded continuously. Vital signs, level of consciousness, Glasgow coma score, and convulsions should be recorded (see Table 13).

Anticonvulsants. Generalized convulsions occur in less than 20% of adults with severe malaria. They frequently mark the start of coma or are followed by neurological deterioration. In adults and children, convulsions can be prevented by a single intramuscular dose of phenobarbital sodium (WHITE *et al.*, 1988a; J. Crawley, personal communication); however, in a trial of prophylaxis with phenobarbitone (20 mg/kg) in Kenyan children, the treated children had a higher mortality rate (J. Crawley, personal communication). Aspiration pneumonia is a common complication of convulsions.

Convulsions should be controlled with diazepam given by slow intravenous injection (adults 10 mg), but in some patients this dose may produce severe respiratory depression. Diazepam emulsion is less irritant to veins. An alternative is intramuscular paraldehyde (adults 0·1 mL/kg). If a plastic syringe is used for paraldehyde, the injection must be given immediately after the drug is drawn up. If injection is to be delayed, a glass syringe must be used. Diazepam can also be given intrarectally (adults 0·5 to 1·0 mg/kg), if the use of injections is not possible. For repeated seizures, chlormethiazole (0·8% solution infused intravenously until convulsions cease), phenytoin (18 mg/kg induction for children, adults 5 mg/kg by intravenous injection over 20 min), or fosphenytoin (same regimen as phenytoin, but note that fosphenytoin sodium 1·5 mg is equivalent to phenytoin sodium 1·0 mg) can be used. Hyperthermia and hypoglycaemia should be excluded.

Although cerebral oedema is not thought to be part of the primary pathology of cerebral malaria, it may develop terminally or during the course of prolonged intensive care if there is fluid overload or gross hypoalbuminaemia.

Deterioration in the level of consciousness and appearance of neurological abnormalities (in the absence of hypoglycaemia) are indications for cranial computed tomography to differentiate intracerebral bleeding from cerebral oedema and cerebral/medullary herniation.

Assisted ventilation may be needed in severe malaria if there is central respiratory failure or pulmonary oedema, and in either case intubation should be performed if possible by an anaesthetist so that there is as little hypercapnia as possible; the pCO_2 should be maintained below 4·0 kPa.

Severe anaemia

In countries where pathogen-free compatible fresh blood is available, transfusion should be considered if the haematocrit of a normally hydrated patient falls below 20%. Fully cross-matched whole blood or packed cells should be used, depending on fluid requirements. Because of the need for clotting factors and platelets, fresh blood is preferable to stored (bank) blood. Transfusion should be carefully monitored and in severely anaemic patients the central venous pressure should be assessed frequently to avoid precipitating hypervolaemic pulmonary oedema (see Annex 3). Provided that renal function is adequate, small intravenous doses of a loop diuretic (e.g., furosemide 20 mg) may be given during the blood transfusion to avoid circulatory overload. In patients with circulatory overload, anaemia is best corrected by exchange transfusion (FULLERTON & TURNER, 1962). Many patients improve after transfusion but repeated transfusions may be required, suggesting abnormally rapid haemolysis of donor erythrocytes. Iron and folic acid supplementation may be necessary when oral medication can be taken, particularly in pregnant patients and in those who may also have hookworm anaemia.

Concern about the dangers of inadvertent transfusion of blood containing HIV, human lymphotropic virus 2, hepatitis viruses, etc. should restrict the use of transfusion in areas where facilities for screening are inadequate. In these situations, blood transfusion is indicated only when clinical signs of shock, cardiac failure, extreme lethargy, and impaired tissue oxygenation are not controlled by colloid infusions and oxygen. Haematocrit may be misleading, as many patients are physiologically compensated for chronic anaemia.

In African children, blood transfusion presents particular problems (see pp. S1/51–S1/52).

Haemoglobinuria and blackwater fever

It is important to continue appropriate antimalarial treatment in patients with proven malaria, despite the hypothetical association between these drugs and haemolysis. Transfusion of fresh blood should aim to maintain a haematocrit above 20% while fluid overload is avoided by monitoring central venous pressure (but see above concerning the danger of HIV etc.). Cross matching may be difficult. The patients should be watched closely. In patients with oliguria and rising blood urea and serum creatinine levels, peritoneal- or haemo-dialysis or haemofiltration may be required (REID *et al.*, 1967; DONADIO *et al.*, 1968; DUKES *et al.*, 1968).

Renal failure

In any patient with severe falciparum malaria, serum creatinine concentrations should be measured daily if at all possible. If the 24 h urine output is below 400 mL and the patient is clinically dehydrated, he or she should be given a fluid challenge of up to 20 mL/kg of 0·9% saline infused over 60 min. In order to prevent fluid overload, lung auscultation and jugular venous pressure measurement and also, if possible, central venous pressure measurements should be performed after every 200 mL of fluid (see Annex 3). The central venous pressure should be maintained between 0 and +5 cm. If there is no urine output after fluid replacement, an intravenous dose of a loop diuretic (furosemide or bumetanide) should be given, 40 mg initially then increasing the dose to 100 mg, 200 mg and 400 mg at half-hour intervals. If there is still no urine flow, dopamine 2·5–5 μg/kg/min should be given through a large peripheral vein. The ef-

ficacy of furosemide and dopamine in preventing or attenuating acute renal failure in malaria has not been assessed, despite their producing an increase in urine output and in creatinine clearance (LUCAS *et al.*, 1977; LUMLERTGUL *et al.*, 1989; DUKE *et al.*, 1994; FLANCBAUM *et al.*, 1994; VINCENT, 1994). Only 5% of anuric patients in Viet Nam responded to an initial diuretic challenge (furosemide, 40–400 mg intravenously), whereas 75% of the oliguric patients responded with increased urine output (TRANG *et al.*, 1992). In view of the limited availability and the high cost of large doses of furosemide, the potential danger associated with the use of dopamine (SEGAL, J. M. *et al.*, 1992), and the risk of delaying dialysis, treatment with these drugs should be considered only in 'uncomplicated' oliguric patients and not in those who are anuric.

If fluid replacement with or without the above-mentioned procedures is ineffective, it is critical that intravenous fluids should be restricted so that the central venous pressure is maintained between 0 and +5 cm H_2O and the body weight falls about 0·5 kg/d. Excessive fluid administration is one of the commonest errors of management.

The indications for dialysis in malaria are not exactly the same as those for other forms of acute renal failure. Experience from Viet Nam has shown that, in addition to the common indications such as hyperkalaemia, metabolic acidosis, fluid overload and anuria, serum creatinine concentration rising rapidly by >2·5–3 mg/dL/d has been one of the most sensitive indicators of the need for dialysis (TRANG *et al.*, 1992) because patients with malaria are hypercatabolic. Some patients will pass small volumes of urine sufficient to maintain fluid balance and, if indications for dialysis do not arise, these patients can be managed conservatively but they will need frequent assessment. Patients with established acute renal failure should be referred if possible to a dialysis centre since close nursing care is needed and, with peritoneal dialysis, large amounts of dialysate (50—60 L/d) need to be prepared. There is also the additional risk of secondary infection associated with the catheter.

Peritoneal dialysis. When dialysis is indicated, the peritoneal catheter* should be inserted in an operating theatre under full sterile conditions. The exchange volume of dialysate** is 1500–2000 mL with a cycle time of 60 min: inflow 10 min, dwell time 30 min, outflow 20 min. This should be modified in each individual as necessary; the duration of exchange of dialysate (standard or shorter dwell period) should be governed by biochemical investigations and fluid overload managed by the use of high hypertonic glucose dialysate** (this is also an excellent way to control hypoglycaemia). Potassium chloride (2–4 mmol/L) must be added to the dialysis solution if the patient is hypokalaemic or normokalaemic. While arrangements for dialysis are being made, patients with very severe hyperkalaemia (above 7 mmol/L or with alterations on the ECG) should be treated immediately with (i) intravenous calcium, or (ii) glucose plus insulin, or (iii) intravenous sodium bicarbonate (**caution**: calcium and bicarbonate must not be mixed). Heparin (200 international units) is usually added to each litre of dialysis fluid to prevent obstruction of the catheter by fibrin clots. The duration of each dialysis session depends on the patient's urine output, serum creatinine concentration and the stage of the disease, and varies from 26 to 82 h (TRANG *et al.*, 1992; Tran Tin Hien, personal communication). Daily reassessment of clinical status, biochemical values (electrolytes, blood urea and creatinine) and 24 h fluid balance are needed. The peritoneal dialysis should be stopped when these variables return to within the normal range and the urine output is above 400 mL/d. However, 30% of dialysed patients required repeated dialysis because of recurrence of renal failure (Tran Tin Hien, personal communication). Complications are rare: infection has been the most frequent. If the dialysis effluent becomes cloudy, a cell count, Gram's stain and culture of peritoneal fluid should be done and antibiotics should be given by both the intraperitoneal and systemic routes. The results of the Gram's stain of concentrated peritoneal effluent guide the initial choice of antibiotic while cultures are awaited.

Haemofiltration. In a recent study in Viet Nam, haemofiltration was shown to be more effective than peritoneal dialysis: haemofiltration corrected acidosis and azotaemia more rapidly and more completely than peritoneal dialysis, and was associated with a shorter duration of treatment (44 h vs. 88 h) (Nguyen Hoan Phu & N. P. Day, personal communication). Unfortunately, facilities for haemofiltration are seldom available in the rural tropics. Therefore, peritoneal dialysis is still preferable for developing countries where malaria occurs (INDRAPRASIT *et al.*, 1988) because this technique is simpler, less expensive, and has other potential advantages. It may reduce the incidence of malaria-associated hypoglycaemia and avoids the risk of parenteral use of an anticoagulant.

Initial doses of antimalarial drugs should not be reduced in patients with renal failure. The doses of quinine and quinidine should be reduced after 2 d in patients with renal failure but doses of chloroquine and artemisinin and derivatives do not need to be altered. The additional clearance of quinoline antimalarial drugs by peritoneal or haemodialysis is small, and need not affect dosage schedules.

Prognosis. Without dialysis, death occurs rapidly in 50% to 75% of patients with acute renal failure (HIEN *et al.*, 1990). If complications can be overcome by dialysis, most patients' renal function will return to normal over a period of several weeks even though during this time the serum creatinine concentration may fluctuate above the normal level. The prognosis in the anuric group was significantly worse both in mortality and rate of recovery of renal function. The mortality rate of severe malaria with renal dysfunction requiring dialysis is around 25% (TRANG *et al.*, 1992) and most patients die during the dialysis, suggesting that they were admitted to hospital too late or the initiation of dialysis was delayed too long.

Pulmonary oedema

Pulmonary oedema may result from fluid overload or increased capillary permeability (adult respiratory distress syndrome or ARDS). To prevent, or at least reduce the chance of, pulmonary oedema developing in patients with severe malaria, the jugular central venous pressure should be maintained between 0 and +5 cm (see Annex 3) by nursing the patients propped up at 45° and by controlling fluid intake. Once pulmonary oedema has developed, treatment should be directed to increasing the inspired oxygen concentration and further reducing the central venous pressure without seriously reducing cardiac output.

The patient should be propped upright and given a high concentration of oxygen by any available method (nasal catheter, face mask, etc.). The simplest and most effective way to reduce central venous pressure is to venesect the patient into a blood transfusion donor bag. Provided the patient has started antimalarial treatment or an antimalarial drug is added to be blood, it can be given back to the patient later either as packed erythrocytes or whole blood. Initially 250 mL of blood can be removed as rapidly as possible and the patient's condition reassessed.

*Any acute dialysis catheter.

**The dialysis solution contains glucose 1·5 g/mL (standard) or 4·25 g/mL (hypertonic) plus (in mEq/L) sodium 135, chloride 101, calcium 3·5, magnesium 1·5, and acetate 45.

This method of venesection helps to overcome objections of medical staff and relatives to removing blood from a patient who is likely to be severely anaemic.

In modern intensive care units, placement of a pulmonary artery catheter with determination of pulmonary artery occlusion pressure may distinguish fluid overload from ARDS. Positive pressure ventilation with PEEP/CPAP (positive and expiratory pressure/continuous positive airway pressure) will usually result in adequate oxygenation until diuresis can be initiated or the ARDS be resolved. In established oliguric renal failure, haemofiltration (arteriovenous or venovenous) can achieve the required fluid loss. SRICHAIKUL *et al.* (1993) suggested that exchange transfusion (see p. S1/41) was a useful adjunct to the treatment of adult respiratory distress syndrome. However, VACHON *et al.* (1990) believed that adult respiratory distress syndrome may be precipitated by exchange transfusion.

Circulatory collapse, shock, hypotension, 'algid malaria' and septicaemia

Patients who become shocked and hypotensive require urgent assessment and management. Possible causes include hypovolaemia resulting from dehydration or massive blood loss (e.g., gastrointestinal haemorrhage or ruptured spleen), pulmonary oedema, and septicaemia. There is no evidence for acute adrenal insufficiency as a cause of this syndrome in severe malaria. Possible sites of infection should be sought (e.g., lung, urinary tract, intravenous injection sites). Blood and other specimens should be obtained for aerobic and anaerobic cultures and an appropriate antimicrobial combination started immediately. Central venous or pulmonary arterial pressure should be monitored where possible. Hypovolaemia should be corrected with an appropriate intravenous infusion, usually 0·9% saline initially followed by a plasma expander (such as fresh blood, plasma, Haemacel®, or, if these are not available, dextran 70). The central venous pressure should not be allowed to exceed 5 cm (Annex 3). If hypotension persists, dopamine can be given preferably through a central or large peripheral vein (DAY *et al.*, 1996; BRUNEEL *et al.*, 1997). An initial dose of 2 μg/kg/min is increased until systolic blood pressure rises to about 80 mmHg. Associated respiratory and renal problems are common. Hypoglycaemia should be excluded. Cardiac arrhythmias are very rare but should be excluded where possible.

Several types of bacterial infection are commonly associated with severe or complicated falciparum malaria: these include pneumonia (aspiration and spontaneous), Gram-negative bacteraemia presumably originating from the gastrointestinal tract, urinary tract infection associated with indwelling catheters, and bacteraemias caused by infected intravenous lines. Intravenous drips and catheters should be inspected regularly and frequently resited.

In patients who may have complicating bacterial infection, cultures of blood, urine, etc. should be obtained if possible. However, those who deteriorate clinically without an identifiable source of infection should be treated empirically with parenteral antimicrobial drugs without waiting for culture results. Combined treatment with benzyl penicillin and 48 h of gentamicin is useful in such circumstances. If it can be afforded, a better combination is cefuroxime or cefotaxime and gentamicin. If high-grade resistance of Gram-negative organisms to gentamicin is known to prevail locally, piperacillin or cefotaxime may be used. If *Pseudomonas aeruginosa* is suspected, ceftazidime may be used. Patients known to have aspiration pneumonia should be treated with clindamycin or benzyl penicillin or, if cost is not a limiting factors, with a combination of piperacillin ceftazidime with gentamicin (48 h of treatment) and metronidazole. Those with urinary tract infection should receive trimethoprim/sulphamethoxazole or ampicillin or, if the urinary catheter can be removed, a single dose of amoxycyllin or gentamicin.

Fluid, electrolyte and acid–base disturbances

Correct management of fluid balance is of enormous importance in patients with severe malaria. Circulatory overload caused by intravenous fluids or transfused blood is extremely dangerous as it may rapidly precipitate fatal pulmonary oedema. Untreated hypovolaemia is equally dangerous as it will lead to hypotension, shock, and underperfusion of the kidney, brain and other vulnerable organs, and lactic acidosis. Initial assessment of each patient is essential, since fluid requirements will vary.

Assessment of hydration status. Many patients will have been febrile for days, sweating profusely and, in some cases, vomiting and passing watery stools. Fluid intake is likely to have been inadequate except for sips of water and patients may become grossly dehydrated and hyponatraemic. Others may have been overloaded with intravenous fluid or blood before they are transferred. The state of hydration can be assessed clinically from dry mucous membranes, skin turgor, temperature of the extremities, postural change in blood pressure, peripheral venous filling and jugular venous pressure (for assessment of venous jugular pressure, see Annex 3).

If the jugular venous pulse cannot be seen clearly and monitored, insertion of a central venous catheter for measurement of central venous pressure should be considered (Annex 3).

History of recent urine output and, in an unconscious patient, examination of urine obtained by urethral catheterization (volume, specific gravity) may be useful. Accurate recording of fluid input and output and daily weighing of the patient is difficult in most hospitals but is very valuable in patients with severe malaria (Table 13). Monitoring of central venous pressure, blood pressure and urinary volume every hour is especially useful in the early stages of fluid management.

Only isotonic intravenous fluids should be used for replacement (0·9% 'normal' saline). In Thailand, a group of 100 patients with cerebral malaria who recovered without developing pulmonary oedema, renal failure, lactic acidosis or other evidence of fluid electrolyte or acid–base inbalance, required an average of 2·4 L of intravenous fluid during the first 24 h of admission. The average output during the same period was 1·6 L. Each patient required on average 10–15 mL of fluid/kg body weight in addition to measured fluid output during the first 24 h of admission (WARRELL, 1987a). However, fluid requirements must not be judged by rules of thumb but based on individual assessment.

Many patients with hyponatraemia are dehydrated and salt-depleted, and so isotonic saline is an appropriate replacement. Hyponatraemia may be 'depletional' through losses in sweat, vomitus and diarrhoea, or 'dilutional' through repletion by water alone (by mouth) or dextrose solution (intravenously). In adults, hypokalaemia is rare.

Acidosis

Metabolic acidosis often develops in severe malaria; in most cases, even with renal failure, it is attributable to lactic acidosis (see below). Arterial oxygen tension is normal in this condition. Lactic acidosis should be suspected if the anion gap (Na^+–[Cl^-+HCO_3^-]) exceeds 10 to 12 mEq/L (OH & CARROLL, 1977).

Sequential studies have shown that lactate levels fall rapidly following the start of treatment. This probably reflects rehydration, cooling and possibly some effects of the antimalarial drugs. Failure of the lactate concentration to fall is associated with a poor prognosis (KRISHNA *et al.*, 1994a). Whether lactic acidosis could be ameliorated by more aggressive fluid administration, use of colloids, or blood remains to be determined.

Table 13. Treatment/progress/observation chart

Ref. ward ______________________
Name ______________________ Bed no.___
Age ______________ Sex ____ Indigenous? [Y | N]
Pregnant? ______________________
Weight (kg) ______________________
Drugs pre-admission ______________________
____
Date & time of admission ______________________

DRUGS (include i.v. fluids, glucose, blood)			Date
			Time
			Hours since admission
drug	dose	route	

SUMMARY OF CONDITIONS ON ADMISSION

Glasgow score	[ ]
Blantyre score	[ ]
Convulsions?	Y / N
Jaundice?	Y / N
Breathlessness?	Y / N
Shock?	Y / N
Oliguria?	Y / N
Haemoglobinuria?	Y / N
Blood glucose	[ ] mmol/L
Haematocrit / haemoglobin	[/] % mg/dL
Parasitaemia	[ ] 10^5/mm^3
CSF: clear?	Y / N
White cells in CSF	[ ] /mm^3

FREQUENCY OF OBSERVATIONS	
(2–4 hourly)	**TEMPERATURE (°C)** (rectal) 41° 40° 39° 38° 37° 36°
(1–4 hourly)	**Infusion fluid** specify, and show duration and volume, e.g. 5% dextrose 500 mL
*	**Urine volume** (mL)
	Input minus **output** (± mL)
(12 hourly)	**Patient's weight** (kg)
(1–8 hourly)	**Pulse rate** (per min)
	BP mm Hg
	Respiratory rate (per min)
	CVP (if placed) (cm)
(4 hourly)	**Level of consciousness** using..............................coma scale
**	**Blood glucose** (mmol/L)
(8–12 hourly)	**Haematocrit** (%)
(8–12 hourly)	**Parasitaemia** ($\times 10^5/mm^3$)
	Able to drink
	Able to sit
	Convulsion
	Other observations (specify)

*Urine volume hourly if catheterized, otherwise when possible.
**Blood glucose should be measured immediately with any deterioration of consciousness or convulsion, otherwise 2–6 hourly.

Tissue perfusion must be improved by correcting hypovolaemia and oxygenation by increasing the inspired oxygen concentration, clearing the airways and, if necessary, supporting ventilation artificially. Correction of acidaemia with bicarbonate should be attempted only if the arterial pH falls below 7·20 and only after correction of any hypovolaemia and hypoxia. Sodium bicarbonate administration entails a considerable sodium load (8·4% solution contains 1 mmol/mL) and may worsen pulmonary oedema. Tris (hydroxymethyl)-aminomethan (THAM) is an alternative which does not contain sodium. Arterial pH should be corrected slowly over 1–2 h. Too rapid correction may precipitate cardiac arrhythmias and a paradoxical central nervous system acidosis. Dichloroacetate, which stimulates pyruvate dehydrogenase principally in skeletal muscle, has proved effective in some cases of lactic acidosis complicating other conditions (STACPOOLE *et al.*, 1988).

Bleeding and clotting disturbances

Full blown disseminated intravascular coagulation with spontaneous systemic bleeding is uncommon in patients with severe malaria in tropical endemic areas (PHILLIPS *et al.*, 1986a), but is relatively common in non-immune patients with imported malaria in the temperate zone. Transfusion of screened fresh whole blood is the best treatment. It can be given by exchange transfusion (GROSS & MELHORN, 1971) in patients who have been overloaded with fluid. Corticosteroids are not indicated for thrombocytopenia. Vitamin K, 10 mg (adult dose) by intravenous injection, can be given if the prothrombin or partial thromboplastin times are prolonged. Drugs which increase the risk of gastrointestinal bleeding (such as aspirin, corticosteroids, non-steroidal anti-inflammatory agents, and heparin) should be avoided as far as possible in patients with severe malaria.

Hypoglycaemia

Hypoglycaemia must be excluded in all patients with severe malaria. Comatose or severely ill adults should be given a test dose of 20–50 mL of 50% dextrose by intravenous injection over 5–10 min if hypoglycaemia cannot be excluded by blood testing. However, the routine administration of 50% dextrose to all patients with severe malaria is not recommended. A wide-bore needle (18–19 gauge) is needed to draw up the viscous solution. Clinical response to dextrose may be dramatic in adults. It is important to realize that quinine-induced hypoglycaemia may develop first after 1–7 d treatment, after the patient has recovered consciousness and appears to be 'cured'. Some children can apparently be protected from quinine-induced hypoglycaemia by continuous infusion of 5% dextrose (TAYLOR *et al.*, 1988). However, this was not effective in adults, and the quantities of fluid required (80 mL/kg/24 h) might cause fluid overload. Continuous infusion of 10% dextrose is preferable, but this regime may result in hyponatraemia unless some saline is added. Hypoglycaemia may recur after an intravenous bolus 'push' of 50% dextrose. Some patients respond to glucagon injection (WHITE *et al.*, 1983a). Dextrose can be given by nasogastric tube, but care should be taken not to give excessive volumes and cause acute gastric distension. If the patient is receiving peritoneal dialysis, dextrose can be added to the dialysis fluid. Prolonged undetected hypoglycaemia can cause permanent, sometimes fatal, neurological damage.

In some situations it may be possible to use the somatostatin analogue octreotide (Sandostatin®) to inhibit quinine-induced insulin release (PHILLIPS *et al.*, 1986b, 1993). This form of treatment is particularly desirable in patients who are overloaded with fluid and will not tolerate further infusion of glucose. Glucagon should be given as its release is inhibited by octreotide.

Blood glucose is checked immediately using a drop of capillary blood from finger-prick or venous blood. BM Stix® 'hypoglycémie' measured by reflectometer is probably the best test, but Dextrostix™ may also be used. Stix must be kept dry. For economy, a stix can be divided longitudinally. If the glucose concentration is more than 5 mmol/L, the test is repeated every 4–6 h unless there is clinical evidence of hypoglycaemia, or quinine/quinidine treatment started in the meantime. If the glucose level is <5 mmol/L, hourly checks are needed. Special vigilance is warranted for high risk patients, such as pregnant women.

Monitoring of the clinical condition and blood sugar must continue even if hypoglycaemia is initially controlled and the patient is receiving intravenous glucose.

Hyperparasitaemia

The use of exchange blood transfusion remains controversial even for presumed non-immune travellers with imported severe malaria presenting to modern hospitals in 'western' countries (see p. S1/41). However, despite the lack of randomized controlled trials there is an increasing impression that this technique can be beneficial in very sick patients.

Conditions for considering exchange blood transfusion

(i) Presumed non-immune patient.
(ii) Persisting high parasitaemia (i.e., more than 10% of circulating erythrocytes).
(iii) Available compatible blood, screened for viruses (hepatitis, HIV, etc.).
(iv) Facilities for safe exchange and monitoring.
(v) Trained staff available.
(vi) Optimal antimalarial chemotherapy already started.

Precise indications for exchange blood transfusion are not established but some tentative criteria are given in Table 11 (p. S1/41).

Adequate preparations for exchange transfusion are necessary, including measurement of haemoglobin, platelets, clotting times, hepatic and renal function and blood glucose. The parasitaemia should be independently verified by a competent person. Urinary catheterization is essential, central venous monitoring is preferred, and facilities for renal dialysis should be available.

The immediate management of the various complications of severe falciparum malaria is summarized in Table 14.

Management of severe falciparum malaria in children

Special problems involved in the management of severe malaria in children include the following items.

(i) *The problem of diagnosis*, including the clinical similarities between malarial acidosis and pneumonia, and the difficulty of distinguishing between cerebral malaria and other diseases causing encephalitis or meningitis.

(ii) *The rapidity with which severe malaria may develop* in a child (the mean duration of symptoms in children with cerebral malaria, for example, is 2 d: see Table 4).

(iii) *The susceptibility of children* to certain clinical developments, including hypoglycaemia, febrile convulsions, dehydration and acidaemia.

(iv) *The lack of facilities* in the clinical settings in which the majority of children must be treated; clinical management policies must be available, affordable and safe if they are to benefit a high proportion of patients.

Table 14. Severe manifestations and complications of falciparum malaria and their immediate management

Manifestation/complication	Immediate management[a]
Coma (cerebral malaria)	Maintain airway, nurse on side, exclude other treatable causes of coma (e.g., hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatments such as corticosteroids, heparin and adrenaline; intubate if necessary
Hyperpyrexia	Tepid sponging, fanning, cooling blanket; antipyretic drug
Convulsions	Maintain airway; treat promptly with diazepam or paraldehyde injection
Hypoglycaemia	Measure blood glucose; give 50% dextrose injection followed by 10% dextrose infusion (glucagon may be ineffective)
Severe anaemia (packed cell volume <15%)	Transfuse fresh whole blood or packed cells if pathogen screening is available
Acute pulmonary oedema[b]	Prop up at 45°, give oxygen, venesect 250 mL of blood into donor bag, give diuretic, stop intravenous fluids; intubate and add PEEP/CPAP in life-threatening hypoxaemia; haemofilter
Acute renal failure	Exclude pre-renal causes, check fluid balance, urinary sodium; if urine output inadequate despite fluid replacement, give diuretic/dopamine; peritoneal dialysis (haemofiltration or haemodialysis if available)
Spontaneous bleeding and coagulopathy	Transfuse screened fresh whole blood (cryo-precipitate/fresh frozen plasma and platelets if available); vitamin K injection
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and Gram-negative septicaemia; give oxygen.
Shock ('algid malaria')	Suspect Gram-negative septicaemia; make blood cultures; give parenteral antimicrobials; correct haemodynamic disturbances.
Aspiration pneumonia	Give parenteral antimicrobial drugs; change position; physiotherapy; give oxygen
Hyperparasitaemia (e.g., >10% of circulating erythrocytes parasitized in non-immune patient with severe disease)	Consider exchange or partial exchange transfusion, manual or haemopheresis

[a]It is assumed that appropriate chemotherapy will have been started in all cases.
[b]Prevent by avoiding excessive rehydration.

(v) *The high prevalence of asymptomatic peripheral parasitaemia* in many populations, in which the presence of parasitaemia does not prove that malaria is the cause of a child's current illness—although the likelihood increases with increasing parasite density.

In many areas where *P. falciparum* transmission is endemic, early recognition and treatment of severe malaria is the responsibility of health assistants, field workers and other staff of peripheral health units. Guidelines for the provisional diagnosis, initial management and prompt referral of children with severe malaria should be based on knowledge of the locally prevailing pattern of malarial complications in children, and on the available facilities, experience and skills.

Effective care of a child with severe malaria requires identification of malaria and of any complication that is present or that develops during treatment (see pp. S1/5–S1/11). Management must include general and supportive measures and antiparasitic drug treatment.

Children's clinical states can change rapidly. A child with severe malaria requires frequent reassessment so that any need or new complication can be recognized and treated.

Coma may be due to cerebral malaria. Other complications of malaria may, however, affect consciousness and should be treated or corrected if possible. These include hypoglycaemia, acidosis, severe anaemia, convulsions, and hyperpyrexia (see below).

Nursing must include all the well-established principles for care of the unconscious child, including frequent turning and careful attention to airway, eyes, mucosae, skin and fluid requirements. The child should be nursed in the semi-prone position.

Management of hypoglycaemia in children

Hypoglycaemia should be suspected in any child with altered consciousness, abnormal behaviour, convulsions, shock or acidosis, even if another cause of the clinical picture is also identified. Hypoglycaemia is associated with a poor prognosis in children with cerebral malaria.

Regular monitoring of blood glucose must be maintained during the initial phase of treatment. The clinical state determines how frequently monitoring should be performed. Children in coma should ideally be monitored every hour: this may be relaxed to every 2 h and then every 4 h if there is no episode of hypoglycaemia and the child is not acidotic. Conscious children with severe respiratory distress should ideally have their blood glucose checked every hour during the acute resuscitation until there is clear clinical improvement. Blood glucose should be checked whenever there is clinical deterioration in a child with severe malaria.

Hypoglycaemia should be treated with dextrose (0·5 g/kg) using a 25% or 50% solution, given over several minutes rather than as a rapid bolus. Hypoglycaemia may be recurrent and profound. Although the use of 10% dextrose for maintenance infusion has been recommended for children at high risk, it is not an effective prophylactic as children may continue to have recurrent hypoglycaemia on this regimen (K. Marsh, personal communication). It is certainly no substitute for careful monitoring of high risk children, i.e., those who are acidotic or comatose. A 10% dextrose solution on its own is not suitable as a maintenance fluid, however; if used, extra sodium chloride should be added or a second intravenous line employed to supply appropriate electrolytes. Interruption of a 10% dextrose infusion carries the risk of rebound hypoglycaemia. The preferable alternative is infusion of 4% dextrose combined with electrolyte solution (see p. S1/53), with careful monitoring of blood glucose concentrations.

If intravenous infusion is not possible, hypoglycaemia can be corrected by giving glucose solution or sugary fluid by nasogastric tube.

Management of respiratory distress in children

The commonest and most important cause of respiratory distress is metabolic acidosis.

Metabolic acidosis. Deep breathing, sometimes accompanied by intercostal indrawing (recession) or indrawing of the bony structure of the lower chest wall, in the absence of localizing chest signs, suggests acidosis (see p. S1/9). Acidosis commonly accompanies cerebral malaria, but it may develop in a child without impaired consciousness; in either case it is associated with an increased risk of death.

Treatment must be aimed at correcting any reversible cause of acidosis, in particular **dehydration** and **severe anaemia**. Because **convulsions** may contribute to lactic acidosis, prevention of further seizures may be beneficial (see below).

The primary management required is resuscitation, with blood or crystalloids (e.g., normal saline) depending on whether the child is severely anaemic. The definition of severe anaemia as a haemoglobin level below 5 g/dL is somewhat arbitrary, and blood transfusion may be appropriate in some children with higher concentrations of haemoglobin. Reasons for restricting blood transfusion to severely anaemic children include both the need to conserve supplies and to avoid the associated risk of HIV and other infections.

If facilities are available, the haemoglobin concentration should be measured. If haemoglobin cannot be measured accurately, the decision about whether the child is severely anaemic must be based on clinical signs, the most useful of which are the presence of severe conjuctival and palmar pallor.

If the haemoglobin concentration is <5 g/dL in a child with respiratory distress or acidosis, a transfusion of screened whole blood, 20 mL/kg, should be given. The urgency of transfusion is based on clinical assessment: if there is nasal flaring and increased respiratory rate only, the transfusion can be given over 4–6 h, but if there is also deep breathing, reduced skin turgor, cool peripheries and disturbed consciousness, the transfusion should be given more rapidly. In this case, the first 10 mL/kg should be given over 1 h and the remaining 10 mL/kg over the next 1–4 h. Severe distress, grunting, gasping or hypotension are indications for emergency resuscitation. Fluid (blood if available or any plasma expander if not) should be given rapidly. Speed is essential and, if adequate venous access cannot be established immediately, infusion through an intraosseous needle into the proximal tibia offers a safe and effective route (see Annex 5).

If the haemoglobin concentration is >5 g/dL, a crystalloid infusion should be given. For children with respiratory distress who are not severely anaemic, the most practical initial fluid is normal saline given in aliquots of 10 mL/kg, the speed of infusion being based on clinical judgement as described above. (Care must be taken not to give excessive fluid and precipitate pulmonary oedema.) The aliquots of fluid can be repeated as often as necessary, based on assessment of clinical and biochemical response.

Ideally, response to blood or crystalloid infusion should be monitored by continuous clinical observation supported by repeated measurements of acid–base status and concentrations of haemoglobin, glucose, urea and electrolytes. In the most severely ill patients it is desirable to monitor central venous pressure (Annex 3). Current, limited, data suggest that titrating fluid input to maintain a pressure between 0 and +5 cm is safe and appropriate. In practice, central venous pressure monitoring will rarely be available and even biochemical monitoring may be difficult; in this situation the patient's response should be judged by clinical observation of rate and depth of breathing, blood pressure and peripheral perfusion (hands and feet).

There is no consensus on the role of bicarbonate in the acute management of metabolic acidosis. Concern over the worsening of intracerebral acidosis may have been overstated. However, in the majority of cases the key to management is urgent correction of underlying problems, particularly hypovolaemia and anaemia. Bicarbonate should probably be reserved for the emergency management of profoundly acidotic children, for instance during resuscitation after a respiratory arrest.

Dichloroacetate (DCA) therapy increases clearance of lactate in rodent models of severe malaria (HOLLOWAY *et al.*, 1995) and in humans (KRISHNA *et al.*, 1994b). However, there is no evidence as yet that this approach has an additional clinically significant effect if fluid management is optimal.

Acute respiratory tract infection. Another important cause of respiratory distress is acute respiratory tract infection. When acute respiratory tract infection and malaria are both common it may be difficult to distinguish them on initial assessment, even when full facilities for investigation are available. Features particularly suggestive of acute respiratory tract infection are the presence of indrawing of the bony structure of the lower chest wall in the absence of deep breathing. Chest radiography is of limited value as a proportion of children with true acute respiratory tract infection have normal chest radiographs on admission. There are 2 potential approaches: (i) either start children with respiratory distress and malaria on parenteral antibiotic therapy in addition to management of malaria, or (ii), preferably, give parenteral antibiotic therapy immediately to those children in whom there is serious doubt about the diagnosis—e.g., those with low parasitaemia, prominent retraction and/or crackles on auscultation—and those without deep breathing. In patients in whom deep breathing is prominent, give fluid resuscitation first and add antibiotic therapy only for those patients who do not show a good clinical response (in practice a small minority).

Management of convulsions in children

Hypoglycaemia should be checked for and treated if necessary, as described above. If the rectal temperature is >39°C, treatment to reduce fever should be given (see p. S1/52). Standard nursing procedures for convulsions are important—maintenance of airway, prevention of injury, avoidance of excessive restraint to movement.

Anticonvulsant drugs are given to treat complex or prolonged fits. The majority of seizures are self-terminating and, to avoid the over-use of anti-epileptic drugs, intervention should be restricted to those whose seizure continues for more than 5 min. Diazepam and paraldehyde are the drugs of choice for initial termination of seizures.

Diazepam should be given intravenously by slow injection at an initial dose of 0·3 mg/kg (rate not to exceed 2 mg/min). Intrarectal administration is an alternative, at a dose of 0·5 mg/kg. Treatment may be repeated cautiously after 15 min if initial treatment fails, but if diazepam has already been administered before admission it is advisable to use an alternative drug. Diazepam is commonly given by intramuscular injection, but this route is not appropriate as absorption is erratic. Diazepam is also frequently given in excessive doses, commonly 5 mg for any small child. For many moderately undernourished children this can represent twice the desired dose and increases the risk of respiratory depression, which may be exacerbated if diazepam has already been given at a peripheral centre. Diazepam-induced respiratory depression may be rapidly reversed by flumazenil, but this is expensive and unlikely to be available in most settings, in which case children should be hand-ventilated by bag and mask or endotracheal tube until spontaneous respiration is achieved.

Paraldehyde (0·2 mL/kg by deep intramuscular injection, or 0·4 mL/kg intrarectally) is a safe and effective anti-epileptic drug; it carries a minimal risk of respiratory depression and may be given in repeated doses, even to children who have already received diazepam. It also has the advantage of being well absorbed from intramuscular injections. The use and availability of paraldehyde in some countries has declined, probably because of perceived problems with storage. However, this is likely to be a problem only with large volumes kept over long periods and individual ampoules offer an improved way of storing the drug. Although a glass syringe is often recommenced, a plastic syringe may be used to administer paraldehyde so long as the injection is given immediately after drawing up the drug, as paraldehyde slowly dissolves plastic. The syringe should not be re-used.

If control cannot be achieved with diazepam or paraldehyde (i.e., if the child continues to convulse or there are repeated recurrences), phenytoin, fosphenytoin (see p. S1/44), or phenobarbitone should be used. They are probably equally effective. Phenytoin is given by intravenous infusion at a rate not exceeding 0·5 mg/kg/min. The drug should not be diluted with dextrose-containing fluids as it precipitates easily. Maintenance, if necessary, is with 5 mg/kg every 12 h. Phenobarbitone should be given in a dose of 20 mg/kg by either intramuscular or slow intravenous injection (rate not to exceed 50 mg/min); maintenance is 4 mg/kg every 24 h if necessary. If control is not achieved with the use of one of these drugs, another should be added.

Prophylaxis of seizures in children with cerebral malaria has been considered; the optimum drug would be safe, cheap and have sustained action over the period of maximum risk. Currently the only widely available drug with these properties is phenobarbitone. A study in Thailand demonstrated a significant reduction in the frequency of fits in a mixed group of non-immune children and adults given 3·5 mg/kg phenobarbitone on admission to hospital (WHITE *et al.*, 1988a). However, this dose produces levels well below those normally considered necessary for effective prevention or treatment or seizures and a subsequent study in Kenyan children showed no significant effect of 10 mg/kg on fit frequency (WINSTANLEY *et al.*, 1992). In 23 children, a dose of 20 mg/kg of phenobarbitone given intravenously produced anti-convulsant blood levels of more than 15 μg/mL within 21 h, which were sustained for 48 h. In a randomized double-'blind' controlled trial of a single intramuscular dose of 20 mg/kg in 329 children with cerebral malaria, the incidence of seizures was significantly reduced and there was some reduction in the incidence of neurological sequelae persisting for less than 3 months. However, case fatality was significantly higher in the phenobarbitone-treated children (P=0·03, odds ratio 2·155 [95% confidence interval 1·095–4·24]) (J. Crawley, personal communication). Until further studies of the mechanism and significance of this phenobarbitone-associated mortality have been carried out, prophylactic phenobarbitone at a dose of 20 mg/kg can no longer be recommended and the major emphasis should be put on recognition and rapid treatment of seizures when they occur. Particularly important in this respect is the observation that up to 25% of children with cerebral malaria having seizures after admission have covert status epilepticus—i.e., electroencephalographic evidence of epileptic activity, with clinical manifestations so minimal that they are likely to go unobserved for long periods (CRAWLEY *et al.*, 1996). Important signs include intermittent nystagmus, salivation and minor twitching of a single digit or a corner of the mouth. Sometimes the only manifestation is an irregular pattern of breathing, and these children often have significant hypoxia and hypercarbia. Terminating the seizure with anti-epileptic drugs usually leads to marked clinical improvement and often to rapid resolution of coma.

Thus children with cerebral malaria require careful and repeated clinical monitoring and the detection of unusual minor signs compatible with seizure activity should lead to a trial of parenteral anti-epileptic drugs, as detailed above.

Management of severe anaemia in children

Because of the increasing dangers of blood transfusion, there have been many recent studies to assess the role of this treatment in the management of severe malarial anaemia.

Respiratory distress in a child with severe anaemia is commonly, but wrongly, attributed to heart failure, with the result that blood transfusion is given slowly and is often accompanied by diuretics (WARRELL *et al.*, 1990; NEWTON *et al.*, 1992). However, the clinical signs in these children are very non-specific, and in the majority there is no evidence of significant cardiac dysfunction. In many cases the main underlying problem is metabolic acidosis. Of 16 children with respiratory distress and severe malarial anaemia in Kenya, central venous pressures (Annex 3) were normal (≤5 cm) in all cases, and all had metabolic acidosis (ENGLISH *et al.*, 1996b). In these circumstances blood transfusion may be life-saving, and excessive caution in the rate of transfusion, or overuse of diuretics, may be dangerous.

Among children with severe anaemia admitted to a Kenyan hospital, blood transfusion appeared to improve survival among children with respiratory distress who had haemoglobin levels below 4·7 g/dL, if the transfusion was given during the first 2 d after admission (LACKRITZ *et al.*, 1992). In a Gambian hospital study of 1143 children with a primary diagnosis of severe anaemia, the mortality rate among transfused patients was 5·5% and that among those not transfused was 13·4% (BREWSTER, 1992).

Decisions about blood transfusion as a possible therapy must be made according to the needs of each individual, rather than according to any formula based on laboratory tests.

The major indication for blood transfusion is respiratory distress in a severely anaemic child, as detailed above. Transfusion may also be indicated in the following situations.

Impaired consciousness with severe anaemia. Reduced oxygen-carrying capacity resulting from severe anaemia may contribute to impaired consciousness. Although data are lacking, it is therefore logical to transfuse such children, even in the absence of respiratory distress. A balance has to be struck between expectation of benefit and considerations of not depleting blood stocks and safety. It may be advisable to transfuse all children with impaired consciousness and a haemoglobin concentration below 5 g/dL. It is even less clear whether there is any advantage in transfusing such children with moderately severe anaemia—i.e., in the range 5–7 g/dL.

Hyperparasitaemia. It can be expected that the haemoglobin level will fall over the following 24–48 h in proportion to the peripheral parasitaemia at the time of starting treatment (and possibly by much more). Therefore a child with a 50% parasitaemia and a haemoglobin level of 6 g/dL can be expected to progress to a haemoglobin level of about 3 g/dL and it is appropriate to transfuse in expectation of this.

Haemoglobin concentration of 4 g/dL or less. The policy of restricting transfusion to severely anaemic children with specific symptoms is important given the high prevalence of severe anaemia, the major shortage of blood for transfusion, and concerns over safety of transfusion. However, there is a point beyond which the chances of subsequent rapid deterioration are too great and, in the absence of clear data on this point, many clinicians would accept a lower cut-off value of 4 g/dL in a young child with acute malaria (as distinct from the situation of an older child with chronic iron deficiency anaemia, who may be relatively asymptomatic and successfully treated with haematinics).

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Two further general points should be made. First, it is probably reasonable to adopt a policy of not transfusing children with haemoglobin concentrations in the 4–5 g/dL range provided there is no respiratory distress or impaired consciousness; but, if such a policy is adopted, each child treated in this way must be **carefully** reviewed over the following 48 h and a small proportion of these children will deteriorate and require transfusion.

Second, the drive to avoid 'unnecessary' transfusions should not deflect attention from the importance of ensuring adequate and safe blood supplies. Blood is probably the ideal fluid replacement for children with malaria and any significant degree of anaemia; current policies are driven by necessity rather than physiological considerations

In African children, transfusion should be reserved for high risk patients with the following clinical features: (i) respiratory distress; (ii) impaired consciousness; (iii) massive parasite loads with low haemoglobin levels.

Children with respiratory distress are, contrary to usual belief, very rarely in congestive cardiac failure. The sicker the child the more rapidly the transfusion needs to be given, and a diuretic is not indicated as many such children are hypovolaemic.

Management of hyperpyrexia in children

Fever may have benefits for the patient with malaria: parasites replicate less rapidly at 39°C than at 37°C, and some immune responses, e.g., antibody synthesis, are accelerated at febrile temperatures. Very high temperatures (>39°C) may, however, be harmful to the host: young children may develop febrile convulsions, and there are increasing metabolic demands as body temperature rises (STETTLER *et al.*, 1992). The temperature should be monitored during treatment for severe malaria, and measured immediately in the event of a convulsion or deterioration of consciousness.

If the rectal temperature is above 39°C, paracetamol should be given either by mouth (20 mg/kg initially, followed by 15 mg/kg every 4–6 h), or per rectum (first dose 30 mg/kg, then 15 mg/kg every 4–6 h). In addition, the mother or guardian should be asked to wet the child's skin with room-temperature water and to fan it repeatedly.

Management of septicaemia in children

If facilities allow, a blood culture should be set up from a child with severe malaria. In (the usual) circumstances in which this cannot be done, the possibility of an additional bacterial infection should be considered. Of 50 Nigerian children with cerebral malaria, 8 had positive blood cultures, due to a variety of organisms (PRADA *et al.*, 1993). Clinical signs are unreliable in differentiating pneumonia from respiratory distress due to severe malaria (see p. S1/6). It is impossible to differentiate confidently between cerebral malaria and meningoencephalitis, and lumbar puncture is contraindicated if there are signs of localized intracranial pathology or papilloedema. Shock may be due in part to bacteraemia.

Any clinical sign of sepsis should be looked for. In a child with breathing difficulty, particular attention should be paid to chest signs of consolidation, and a chest radiograph taken if possible. Antibiotics should be given to (i) any child with localized signs suggesting bacterial infection, (ii) any child with severe respiratory distress in whom deep breathing does not rapidly improve with correction of dehydration or anaemia (see above), (iii) any child with shock, and (iv) a child in coma or with encephalopathy in whom lumbar puncture has not been done.

If an organism is identified by culture, appropriate treatment can be given. Otherwise, the best available combination of antibiotics should be used—e.g., chloramphenicol 25 mg/kg every 6 h intravenously/orally/by nasogastric tube, or 60 mg/kg benzyl penicillin intravenously every 6 h together with gentamicin 5 mg/kg once daily for 48 h.

Management of raised intracranial pressure in children. Raised intracranial pressure is a feature of cerebral malaria in African children and in over 50% of cases pressures exceed levels that would normally be considered indications for specific treatment. Cerebral herniation secondary to very high levels of intracranial pressure in cerebral malaria is responsive to osmotic diuretics (NEWTON *et al.*, 1996). However, the following points need to be considered. Deaths and sequelae are particularly associated with a small group of children who develop severe intracranial hypertension. It is not possible to identify this group without direct intracranial pressure monitoring and in such a group osmotic diuretics were unable either to prevent the development of severe intracranial hypertension or to control it even when timing of treatment was optimized (NEWTON *et al.*, 1996). It seems likely that severe intracranial hypertension (as opposed to a milder degree) results from extensive damage of neural tissue. Although intracranial hypertension is responsive to osmotic diuretics, there is little evidence that this is decisive in affecting outcome. It seems likely that intracranial hypertension in children results from transient self-limiting brain swelling secondary to vascular factors. Thus current evidence does not support the routine use of osmotic diuretics on an empirical basis in cerebral malaria. Similarly there are no data to support the use of other agents such as corticosteroids, which had no beneficial effect in adults with cerebral malaria (WARRELL *et al.*, 1982; WARRELL, 1999) and are rarely useful in diffuse encephalopathies (FISHMAN, 1982) or in the resolution of cytotoxic oedema secondary to ischaemia or hypoxia. Thus, without clear evidence of benefit from specific interventions, the therapeutic approach to raised intracranial pressure in cerebral malaria should concentrate on the following supportive measures.

(i) The patient should be nursed with the head in the midline as this increases venous drainage. It is essential that a nasogastric tube on free drainage be present to avoid the risk of aspiration of stomach contents.

(ii) Seizures lead to a rise in intracranial pressure. Prolonged and repeated seizures may have a damaging effect in their own right and it seems likely that this may be synergistic with any effect of acute rises in intracranial pressure. Seizures should be terminated promptly with diazepam 0·3 mg/kg by slow intravenous injection (not to exceed 2 mg/min) or paraldehyde 0·2 mL/kg by intramuscular injection. Recurrent seizures may require further doses but the repeated use of diazepam requires caution. Respiratory depression following diazepam may be reversed by intravenous flumazenil but this is expensive and unlikely to be available in most settings. Paraldehyde has little risk of respiratory depression. Use of paraldehyde has decreased, probably because of worries over its stability. However, if paraldehyde is stored according to instructions, and particularly if available in sealed ampoules, it is a safe and effective anti-epileptic. Failure to control seizures with repeated diazepam or paraldehyde requires the use of a longer-acting agent. Phenytoin (18 mg/kg by slow intravenous infusion) or fosphenytoin is effective. It may be necessary to use two agents if adequate control is not achieved with one.

(iii) Hypoglycaemia must be detected and treated rapidly (see pp. S1/49–S1/50).

(iv) Severe anaemia should be corrected (see pp. S1/51–S1/52). Although there are few data to guide policy, it is probably reasonable that all children with cerebral malaria and a haemoglobin level below 5 g/dL should be

transfused with 20 mL/kg whole blood over 4 h. Although the volume load may increase intracranial pressure, in practice the rise is small and is offset by improved cerebral perfusion pressure (J. Crawley, personal communication). There are currently no data to indicate whether transfusion of children whose haemoglobin level is in the range 5–8 g/dL is of benefit.

(v) Acidosis should be corrected with urgency (see p. S1/50). This will require transfusion of blood or crystalloid, depending on the relative contribution of anaemia and hypovolaemia. Although there may be concern over volume loading children who are likely to have a raised intracranial pressure, restoration of circulating volume, adequate tissue perfusion and control of acidosis should take precedence. It should be noted, however, that hypocapnia associated with hyperventilation stimulated by metabolic acidosis may help to attenuate raised intracranial pressure. Mechanical ventilation may result in temporary or permanent increases in arterial pCO_2 which may adversely affect intracranial pressure. If facilities permit, it is desirable to monitor central venous pressure in the most severely ill children (Annex 3).

(vi) Lumbar puncture in children with cerebral malaria. It is essential to exclude meningitis in any child with signs of neurological involvement. This includes any child who has any disturbance of conscious level and any child under the age of one year with seizures (over the age of one year, children with a single febrile seizure who recover full consciousness rapidly and have no other sign of severe illness may not require a lumbar puncture). Meningitis should be excluded even if the diagnosis of cerebral malaria seems clear-cut. For example, on the Kenyan coast 2% of comatose children with parasitaemias above 10 000/μL have acute bacterial meningitis (K. Marsh, personal communication). However, raised intracranial pressure is regarded as a contraindication to lumbar puncture and normal practice where facilities exist for computed tomography scanning is to begin immediate empirical therapy and exclude brain swelling before proceeding to a lumbar puncture. This is clearly impracticable in most places where cerebral malaria is treated. In these circumstances, a reasonable policy is to do a lumbar puncture in all children with cerebral malaria, on the grounds that the risks of precipitating coning are likely (though not proven) to be less than the chance of missing the diagnosis of acute bacterial meningitis. An alternative policy has been suggested, which is to begin immediate empirical treatment using the locally appropriate parenteral regime for acute bacterial meningitis in addition to normal management of cerebral malaria; lumbar puncture can then be carried out when the child is neurologically stable, usually between 24 and 48 h after admission, and antibiotics discontinued if the cerebrospinal fluid cell count is normal. The disadvantage of the second policy is that large quantities of antibiotics will be used unnecessarily on the great majority of children with cerebral malaria. **Under no circumstances should a compromise procedure of delaying lumbar puncture without full antibiotic cover be adopted.**

Fluid and feeding requirements

Many children with severe malaria will have not eaten or drunk for several hours, and fever and tachypnoea may have led to further fluid loss. Volume depletion may exacerbate acidosis.

Hydration should be assessed and any obvious fluid depletion corrected using an isotonic solution such as normal saline. For maintenance fluid therapy in a child not drinking or eating (e.g., an unconscious child), an intravenous fluid containing electrolytes and glucose—e.g., half-strength Darrow's, half-strength Hartmann's, or 0·18% normal saline containing 4% dextrose—should be given.

Maintenance infusion rates may be calculated as follows. For the first 10 kg body weight, give 4 mL/kg/h; for the next 10 kg body weight, give 2 mL/kg/h; for each additional kg body weight, give 1 mL/kg/h.

The most widely available fluid is 0·18% saline containing 4% dextrose; this is probably an acceptable alternative (**it is not an appropriate resuscitation fluid**). However, this fluid supplies little sodium and no potassium and both hyponatraemia and hypokalaemia may develop. In the majority of children this is of limited significance as oral fluids can be commenced quickly. In the minority who require sustained intravenous hydration, supplementation of sodium and potassium should be guided by measurement of renal function and plasma electrolytes. Previous recommendations that children with severe malaria should be given restricted fluids are not appropriate in view of the high prevalence of dehydration and the role of hypovolaemia in the development of metabolic acidosis. Concerns over the possibility of inappropriate secretion of antidiuretic hormone (vasopressin) are probably misplaced as there is no evidence that this is other than a rare event (ENGLISH *et al.*, 1996c). The one group for whom an argument can be made for restricted fluids are those children with cerebral malaria without evidence of metabolic acidosis. Intracranial hypertension is a feature of this encephalopathy and standard management of intracranial hypertension would normally include restricting fluids to approximately 60% of normal requirement. However, even in this group, ensuring adequate circulating volume and appropriate management of acidosis and severe anaemia should take precedence over concern that a fluid load may worsen intracranial hypertension.

In a child who requires intravenous therapy for more than 24–36 h, nutritional needs should be attended to. If a gag reflex is present and the patient can swallow, give sips of milk/sugar solution or thin gruel every hour. If a gag reflex is not present, or the child cannot swallow, a nasogastric tube should be inserted and boluses of milk/sugar solution given every 1–2 h, calculating volumes according to the intravenous schedule given above. The child's head must be kept elevated 15°C above horizontal, and the fluid administered slowly. Once this route of giving fluids is established, intravenous fluids can be stopped.

Renal failure is rare in children. In those presenting with oliguria and dehydration, urine examination usually reveals high specific gravity, low urinary sodium, and normal urinary sediment, indicating simple dehydration. After careful rehydration, urine will begin to flow in most cases. If the urinary output is less than 4 mL/kg body weight in the first 8 h despite rehydration, furosemide can be tried initially at 2 mg/kg then doubled at hourly intervals to a maximum of 8 mg/kg (given over 15 min). However, furosemide may not prevent renal failure in the oliguric patient (LUCAS *et al.*, 1977). If the child fails to produce more than 4 mL/kg body weight of urine at the end of 16 h despite adequate rehydration, strict fluid balance should be instituted, with input equal to urinary output plus calculated insensible losses, and the patient transferred to the nearest hospital with dialysis facilities. Where facilities for monitoring and maintenance of adequate sterility exist, fluid balance in severe malaria should be adjusted by direct measurement of the central venous pressure through a central venous catheter. If this is not possible, careful and frequent examination of the jugular venous pressure, blood pressure and chest is essential.

Antimalarial chemotherapy

In children with severe falciparum malaria, antimalarial drugs should, if possible, be given by intravenous infusion. Oral administration of the drug should replace parenteral therapy as soon as possible. Where parenteral therapy is not possible, suppository formulations of artemisinin or artesunate should be considered. Children should be weighed and the doses of antimalarial drugs

should be calculated on a mg per kg basis. Antimalarial chemotherapy is summarized in Tables 8, 9 and 10.

The principles of antimalarial drug administration are the same for children as for adults. Oral medication should not be attempted in unconscious children, who should be referred to facilities where parenteral therapy is available as soon as possible.

Quinine. Quinine may be given by intramuscular injection to children if circumstances do not permit intravenous infusion. The injection should be given into the anterior or lateral thigh, to avoid the risk of injury to the sciatic nerve. Concentrated, unbuffered solutions of quinine (30 mg/mL) are painful when given by intramuscular injection to children. Buffered or more dilute solutions (60–100 mg/mL) are preferable (MANSOR *et al.*, 1990). This can be achieved by diluting quinine 1 to 5 with sterile water for injection. Chloroquine, but not quinine, can be given by subcutaneous injection. Precise dose determination on the basis of weight is mandatory for the use of parenteral antimalarial drugs in children.

It is unusual for severe falciparum malaria to have a protracted course in children. The majority of those who recover from cerebral malaria regain consciousness within 36 h (MOLYNEUX *et al.*, 1989b). For a child requiring parenteral quinine for longer than 3 d, the dose of quinine should then be reduced by one-third or one-half to avoid possible cumulative toxicity. By this stage it is usually possible to give quinine, fluids and nourishment by nasogastric tube.

Management of severe falciparum malaria in pregnancy

Management

Non-immune pregnant women are at increased risk of severe disease if infected with *P. falciparum* (see p. S1/18).

Pregnant women with severe malaria should be transferred to intensive care if possible. Monitoring of uterine contractions and fetal heart rate may reveal asymptomatic labour and fetal tachycardia, bradycardia, or late deceleration in relation to uterine contraction, indicating fetal distress (LOOAREESUWAN *et al.*, 1985a). Once labour has started, fetal or maternal distress may indicate the need to shorten the second stage by forceps, vacuum extraction or even caesarean section (LAWSON, 1967). Particular dangers are hypoglycaemia (see p. S1/19), which may be asymptomatic for the mother but can cause fetal bradycardia; hyperpyrexia, which may be associated with fetal distress; acute pulmonary oedema; and post-partum haemorrhage (LOOAREESUWAN *et al.*, 1985a).

A woman who goes into labour severely anaemic or overloaded with fluid may develop acute heart failure or pulmonary oedema after separation of the placenta (associated with increased blood volume and peripheral vascular resistance). If the haematocrit is below 20%, transfusion with packed red blood cells should be considered, and the need for intravenous diuretics and fluid restriction should be frequently assessed. An increase in respiratory rate or dyspnoea is an ominous finding and should prompt immediate clinical re-examination, measurement of blood glucose concentration, and chest radiography. Since pregnant women and their babies are at high risk of a fatal outcome, all aspects of care must be as detailed and vigilant as possible.

Since severe hypoglycaemia may be asymptomatic in pregnant women (LOOAREESUWAN *et al.*, 1985a) and may produce symptoms which are easily confused with cerebral and other severe forms of malaria, it must be excluded in all cases of severe malaria, by measurement of the blood glucose concentration. If this cannot be done, a therapeutic test with 50% dextrose (25–50 mL infused intravenously over about 5 min) should be used. Recurrent severe hypoglycaemia is a difficult problem in some cases. It may not be prevented by continuous intravenous infusions of 5% or even 10% dextrose. Repeated use of intravenous hypertonic 50% dextrose may lead to circulatory overload and, in the presence of hyperinsulinaemia, to electrolyte shifts (resulting in, e.g., hypokalaemia), as in the treatment of diabetic coma. Dextrose solution can be given through a nasogastric tube to unconscious patients.

Table 15. Characterization of severe malaria and its identification at different levels of health care

	Peripheral or community level[a]	Intermediate level[a]	Central hospital level[a]
Clinical assessment			
Difficulty in talking, sitting up, standing or walking	+	+	+
Cerebral malaria	+[b]	+[b,c]	+[b,d]
Vomiting	+	+	+
Respiratory distress (acidosis)	+	+	+
Bleeding and clotting disorders	+	+	+
Severe anaemia	±[e]	+	+
Jaundice	±	+	+
Hyperpyrexia	+	+	+
Circulatory collapse	–	+	+
Haemoglobinuria	–	+	+
Hypoglycaemia	–	±	+
Fluid, electrolyte, acid–base disturbances	–	±	+
Complicating/associated infections	–	±	+
Pulmonary oedema	–	±	+
Exclusion of other diagnoses	–	±	+
Parasitological diagnosis			
Hyperparasitaemia	±[f]	±	+

[a]Possibility of assessment at this level: +, yes; ±, sometimes; –, usually no.
[b]Confusion, drowsiness, convulsions.
[c]Exclude meningitis (neck rigidity, photophobia).
[d]Exclude meningitis (lumbar puncture).
[e]Using a simple colour chart (now available), severe anaemia can be diagnosed at the periphery.
[f]Indicates need for parenteral treatment but not necessarily the diagnosis of severe disease (see p. S1/5). Where a special malaria clinic is established this might be possible, but generally at this level it is not.

Chemotherapy

In high doses, quinine is oxytocic to the pregnant uterus, causes frequent meconium emissions during labour and is embryo- and feto-toxic and teratogenic (ONNIS & GRELLA, 1984). However, its use for life-threatening malaria in pregnancy has been advocated since the 19th century and, in a study of women who were more than 30 weeks pregnant, the initial intravenous infusion of quinine was not associated with uterine stimulation or fetal distress (LOOAREESUWAN *et al.*, 1985a). The major adverse effect is hypoglycaemia (WHITE *et al.*, 1983a) (see p. S1/19). Quinine pharmacokinetics are altered in pregnancy, with reduction in the total apparent volume of distribution and shortening of the elimination half-time compared with other adults (PHILLIPS *et al.*, 1986c). These changes are not of sufficient magnitude to warrant changes in dose recommendations but they do emphasize the importance of a slow rate-controlled infusion and a thrice daily regimen with quinine therapy. Quinine is excreted in breast milk but the total amount of drug consumed by the infant is unlikely to be significant. Recommended doses are given in Table 8.

Although high maternal doses of chloroquine during pregnancy may cause nerve damage in the fetus, extensive clinical experience with normal prophylactic and therapeutic doses indicate that chloroquine can safely be used in pregnancy (ONNIS & GRELLA, 1984; WOLFE & CORDERO, 1985).

Sulphonamide/pyrimethamine combinations are valuable in areas of Africa and the Indian subcontinent, where most strains of *P. falciparum* are still sensitive to these drugs, and can be used if quinine is not available. Recommended doses are given in Table 8. A curative dose of an oral sulphonamide/pyrimethamine combination given at the first attendance at the antenatal clinic (second trimester) and again at the beginning of the third trimester resulted in a significant reduction of both peripheral and placental parasitaemia, and no side effect was noted in either the mothers or the infants (SCHULTZ *et al.*, 1996) (see also pp. S1/65–S1/66). In over 80 pregnant patients treated with artesunate or artemether, both these drugs were shown to be effective and safe (MCGREADY *et al.*, 1998). The infants at delivery were all normal. There is no reason to date to withhold these drugs from pregnant women with life-threatening severe malaria. Recommended doses are given in Table 10.

Identification and management of severe malaria at various levels of health care

Peripheral health units will inevitably face severe and complicated cases of malaria which must be immediately recognized (or suspected) and managed appropriately. WHO and UNICEF have worked together to develop an integrated care management approach to the leading killer diseases of young children that can be effectively managed, including malaria. It provides a system that health workers can follow to consider quickly all of a child's main symptoms and identify need for urgent referral or management of severely ill children.

If patients with severe and complicated malaria are to receive the best possible treatment, there must be an effective referral system from the community to the secondary and tertiary health facilities that have the capacity, supplies and well-trained staff appropriately to manage severe disease. Responsibility at each level will vary according to the human and financial resources available to manage the problem. A referral system should not, however, be a set hierarchical procedure. Patients should be referred to the facility that can adequately manage the case and all health personnel must know the limitations that exist at each level of the health system.

To illustrate the principles of a referral system, health care facilities at 3 levels may be considered. How staff at each of these levels can approach the diagnosis of patients with severe malaria according to their training and clinical competence is outlined in Table 15.

Facilities able to provide only minimal care

Such facilities may be found at the peripheral or community level. Commonly there is a paid health post attendant, or a community health worker who may be a volunteer. Usually, such persons have had limited training and are not expected to be able to elicit or interpret a detailed medical history, carry out more than a superficial examination, or apply sophisticated clinical judgement. By definition there is no laboratory facility and at present only oral medications or suppositories may be given.

The principal responsibility at such facilities is prompt diagnosis and adequate treatment. The personnel involved should be able to recognize certain features of severe and complicated malaria, should be able to know how to bring down the temperature by tepid sponging and the use of antipyretic drugs, should be able to give a first dose of a blood schizontocidal drug by mouth or rectally, and should be able to recognize patients requiring referral elsewhere and give appropriate guidance and assistance where possible.

Criteria that could be applied by a community health worker or aid post orderly for referral to a facility intended to provide appropriate care include (i) vomiting and inability to retain oral medication; (ii) inability to eat, drink or breast feed; (iii) failure to respond to initial treatment; (iv) difficulty in talking, sitting up, standing or walking (without obvious cause); (v) unexplained heavy bleeding; (vi) passage of small quantities or no urine, or passage of unusually coloured urine; (vii) a change of behaviour, confusion or drowsiness; (viii) altered consciousness or coma; (ix) convulsion(s); (x) jaundice and/or severe anaemia; (xi) circulatory collapse or shock; and (xii) abnormal breathing.

The management of the patient at this level, before referral or if referral is not possible, is described in Table 8.

Facilities able to provide intermediate care

Such facilities are found in a wide range of geographical and epidemiological circumstances, including isolated areas at the periphery with poor accessibility especially during the peak malaria transmission period, although generally such facilities are dispensaries and health centres. This means that referral might not be possible and so health workers may have to continue treatment of the severely ill patient.

Parasitological diagnosis may be available as well as other laboratory facilities; personnel are expected to perform simple examinations and exercise some clinical judgement. Suppositories and parenteral treatment by intramuscular or subcutaneous injection are available but, by definition, not intravenous therapy.

There are 3 major principles for the management of severe malaria at this level (Table 9): (i) recognition/confirmation of severe malaria; (ii) provision of an antimalarial drug by the most expeditious route; and (iii) rapid referral when necessary and possible.

At this level patients with coma, jaundice, severe anaemia, oliguria and breathing problems should be referred after the diagnosis of *P. falciparum* malaria is confirmed by laboratory examination and after antimalarial therapy has been given. Patients with convulsions and hyperpyrexia can be managed at this level. However, referral of severely ill patients should not be delayed by diagnostic procedures after initial malaria treatment has been given. The choice of antimalarial drug will depend

on national policy based on the local parasite sensitivity pattern and other factors.

Facilities able to provide maximal possible care

In these facilities the appropriate management of severe and complicated malaria, as described in this publication, should be possible. Staff should be competent to take a detailed history, make a comprehensive physical examination and carry out various investigations. Basic parasitological, biochemical, haematological, bacteriological and radiographic services should be available.

A wide range of antimalarial drugs should exist in these facilities and, by definition, intravenous therapy is possible (see Table 10). Additional support services and professionals should be available to manage various complications of the disease.

Common errors in the diagnosis and treatment of severe falciparum malaria

Failure to establish history of exposure to malaria

A diagnosis of malaria may not be considered because of failure to elicit a history of travel to an endemic area (especially if it took place during the previous year). This error is particularly common in temperate climates, but also occurs within endemic regions, where an individual moving from a low-transmission area (e.g., large city, high altitude) to a high transmission area is at increased risk of severe malaria. Indigenous people returning from 2 or more years spent in a temperate country are also at risk. Common misdiagnoses in the temperate areas are influenza, viral encephalitis, hepatitis or psychosis (see Table 6). Misleading presenting symptoms, such as diarrhoea, may contribute to the misdiagnosis. If malaria is not considered, it is unlikely that a properly stained thick blood film will be examined, but malaria may sometimes be diagnosed from the routine haematological film. If an exotic virus infection (Lassa, Marburg, Ebola, Hantaan, Congo-Crimean haemorrhagic fever) is suspected, the patient may be isolated and denied basic investigations for fear of contamination.

Malaria must not be excluded from the differential diagnosis because the patient was taking prophylactic drugs, for these are not always completely protective. Short airport stop-overs, waiting on the airstrip with the aircraft's doors open and residence near international airports may allow sufficient exposure to infected mosquitoes.

Failure to consider modes of infection other than mosquito bites

A diagnosis of malaria may not be considered because a history of blood transfusion, tissue/organ transplantation or the use of contaminated needles is neglected. Nosocomial infection through contaminated intravenous injection has been reported.

Technical problems

The diagnosis of malaria may be missed for purely technical reasons: inadequate blood film, faulty microscope, dirty slides, wrong buffer pH, contaminated/deteriorated stains, inexperienced microscopist, failure to examine the slide, brevity of examination, faulty labelling, storage of blood in anticoagulant before the smear is taken. Thin blood films dried slowly in a very humid environment, or fixed in diluted methanol, are difficult to interpret. Sometimes a mixed infection may be misdiagnosed: e.g., *P. falciparum* may not be identified in the presence of *P. vivax*.

Failure to diagnose associated or complicating conditions

The diagnosis of malaria may be overlooked even in a malaria endemic zone—e.g., during the meningitis epidemics in sub-Sahelian Africa, cholera epidemics in Bangladesh, and in patients presenting with pneumonia in Papua New Guinea. Conversely, the discovery of malaria parasites in the blood film should not close the physician's mind to additional or alternative diagnoses (see pp. S1/31–S1/32 for discussion of differential diagnosis). Particularly in hyperendemic areas, parasitaemia may not be the cause of major symptoms such as fever. The following conditions were discovered in comatose patients with asexual *P. falciparum* parasitaemia in eastern Thailand: meningococcal, pneumococcal and cryptococcal meningitis; viral hepatitis; Gram-negative septicaemia; insecticide poisoning; eclamptic toxaemia; and ruptured spleen.

Patients with the classical features of 'algid malaria' (shock, hypotension, constricted cyanotic extremities, coma, oliguria, etc.) frequently have complicating Gram-negative bacteraemias which must be treated with appropriate antimicrobial drugs if the patient is to survive. Malaria may coexist with pneumonia or pulmonary tuberculosis.

Missed hypoglycaemia

Severe hypoglycaemia is common in patients with severe falciparum malaria. Pre-treatment hypoglycaemia is common in children with severe malaria, and may occur also in adults, especially in pregnancy. Hypoglycaemia induced by quinine or quinidine treatment may occur during treatment and is particularly common in pregnancy. Hypoglycaemia cannot be identified from clinical examination alone, because all the signs of hypoglycaemia may be mimicked by those of malaria. In any patient with malaria and altered behaviour or consciousness, or convulsion, blood glucose should be checked immediately; if this cannot be done, or if the result is likely to be delayed, the patient should be assumed to be hypoglycaemic and should be given glucose.

Errors of antimalarial chemotherapy

Delay in starting treatment, despite clinical suspicion of severe malaria, because the blood film is negative, or because the 'drug of choice' is not available. For example, if parenteral quinine is not available to treat a patient with falciparum malaria acquired in an area with chloroquine resistance, treatment should be started with any available antimalarial drug. In this situation quinidine gluconate injection, used for cardiac arrhythmias, is a good substitute for quinine; chloroquine may be life-saving, even in chloroquine-resistant infections; mepacrine may be available in some countries (used for taeniasis or giardiasis); and a variety of antibiotics (e.g., cotrimoxazole, tetracycline, azithromycin, fluoroquinolones, clindamicin etc.) have some antimalarial activity. Most antimalarial drugs are stable in solution for many years at ambient temperature, and so an outdated drug can be used in the absence of any in-date material. However, outdated tetracycline may be nephrotoxic.

Quinine is not bacteriostatic, and so starting quinine treatment does not interfere with blood cultures.

Unjustified withholding of an antimalarial drug because of exaggerated or unfounded fears of toxicity—e.g., quinine in pregnant women or patients with haemolysis, hypoglycaemia, etc.

Dosage not correctly calculated because the patient was not weighed.

Inadequate dosage. Failure to use a loading dose of quinine: an initial dose of quinine dihydrochloride 10 mg/kg/d will often fail to raise the quinine level beyond the minimal inhibitory concentration even in patients with malaria complicated by renal or hepatic dysfunction.

Excessive dosage. Dosage of antimalarial drugs is uncertain in grossly obese patients and at extremes of age.

Miscalculation of dose because of confusion between the dose of **base** and **salt** (see Annex 2).

Dangerous route of administration. Some authorities still recommend that the initial dose of quinine should be given diluted in 10–15 mL of isotonic fluid and in-

jected intravenously over 10–15 min. This is dangerous as very high plasma concentrations of quinine may occur during the distribution phase (WHITE *et al.*, 1983b).

Inappropriate route of administration. Ideally, all patients with severe malaria should receive intravenous antimalarial therapy initially. Intramuscular, nasogastric, oral or rectal routes should be used only when intravenous treatment is not possible (see Tables 8, 9 and 10), but intramuscular artemether has proved as effective as quinine in adults with severe malaria. Chloroquine can be given safely by intravenous infusion or by the intramuscular or subcutaneous routes, provided that appropriate schedules are used (see Tables 8 and 9).

Misjudgement of severity. Even if malaria is suspected or actually diagnosed, the patient may be inappropriately treated because of faulty clinical assessment. For example, a jaundiced, dehydrated, oliguric or nauseated patient may be sent home on oral antimalarial treatment. Patients with falciparum malaria may deteriorate very rapidly. Deaths have occurred within 24 h of the first symptom.

Failure to elicit a history of recent chemotherapy. This creates the danger of overdosage. Where possible, the urine should be tested for antimalarial drugs.

Unjustified cessation of treatment. On current evidence, it is unjustified to stop quinine because a patient develops hypoglycaemia or severe haemolysis with haemoglobinuria, or because a pregnant woman goes into premature labour or there are signs of fetal distress. The dangers of uncontrolled falciparum infection outweigh the equivocal or controllable side effects of quinine.

Failure to control the rate of intravenous infusions. Where nursing care is inadequate, intravenous infusions of antimalarial drugs may be allowed to run in very rapidly. This can be fatal.

Failure to prevent cumulative effects of antimalarial drugs. In patients who require prolonged intravenous quinine for treatment, the drug may accumulate, especially when there is renal or hepatic dysfunction.

Failure to switch patients from parenteral to oral treatment as soon as they can swallow.

Unnecessary continuation of parenteral or oral treatment after clearance of parasitaemia or in patients with persistent coma (or other severe manifestations) despite 14 d of antimalarial chemotherapy.

Failure to recognize that the therapeutic priorities in severe malaria are different from those in uncomplicated malaria.

Errors of fluid and electrolyte replacement

Many patients with severe malaria will arrive in hospital dehydrated, but others may be overloaded with fluid if they have already received intravenous fluids or blood transfusions at another hospital or clinic. Each patient must be assessed individually. Severely dehydrated and hypovolaemic patients who are deprived of fluids will become hypotensive, shocked and oliguric and progress to lactic acidosis and acute renal tubular necrosis. Well hydrated patients who are given large volumes of intravenous fluid, especially hypertonic fluids, bicarbonate, 50% dextrose, mannitol or blood, may well be precipitated into irreversible pulmonary oedema or electrolyte disturbances, commonly hyponatraemia and hypokalaemia.

Common errors are failure to examine the patient thoroughly (e.g., skin turgor, jugular venous pressure, postural change of blood pressure, peripheral perfusion [hands and feet], urine output, and specific gravity), failure to maintain fluid balance charts (and/or to weigh the patient daily; Table 13), excessive and unnecessary use of hypertonic solutions, too rapid transfusion without close clinical supervision and diuretic cover, failure to measure urine output (undisciplined or incontinent urination or failure to pass a urethral catheter), failure to include blood, bicarbonate, mannitol, 50% dextrose boluses and the fluid vehicle for antimalarial drugs in fluid balance calculations, and failure to ask patients or relatives about fluid input and output during the 48 h before admission. In seriously ill patients, central venous pressure monitoring is invaluable for monitoring fluid replacement (Annex 3).

In children who are unable to eat or drink, fluid replacement must include sufficient glucose to prevent the development of fasting hypoglycaemia.

Venous access is crucial in sick patients. Valuable veins in upper and lower extremities must not be squandered by inexpert staff. Patients must be adequately restrained so that they cannot pull out intravenous lines. Venous cannulae must be well secured with adhesive tape and the cannulated limb splinted to prevent flexion at the site of cannulation. In children, scalp vein cannulae can be secured in a plaster of Paris mould. Venous cut-downs, which nearly always lead to complications, should never be necessary. The femoral vein, located below the inguinal ligament **medial** to the femoral pulse, can be a life-saving route of therapy (Annex 4). Hypertonic solutions will thrombose veins. If no vein can be found in an emergency, infusion can be started intraperitoneally and, in children, subcutaneously or intraosseously (tibia)(Annex 5).

Nursing problems

Failure to nurse comatose patients on their sides will lead to aspiration pneumonia, and failure to turn them every 2 h or so, or allowing them to lie in wet beds, will promote bed sores (decubitus ulcers). Hyperthermia is dangerous: it causes febrile convulsions in children and may cause premature labour and fetal distress in women in late pregnancy. Temperature (preferably core, i.e., rectal, temperature) must be monitored frequently. If it rises above 39°C, the patient must be cooled by vigorous tepid sponging and fanning or cooling blankets and use of antipyretic drugs. In an intensive care unit, body temperature can be lowered by cooling respired gases or intravenous peritoneal dialysis/haemofiltration fluids.

Errors in patient management

Delay in considering obstetrical intervention in women with severe malaria in late pregnancy. When the condition of a woman with malaria in the last trimester of pregnancy deteriorates or signs of fetal distress develop, obstetrical intervention (induction of labour or caesarian section) should be considered if the response to medical treatment (cooling, etc.) is unsatisfactory. There is a danger of post-partum pulmonary oedema in women who are overloaded with fluid.

Delayed or premature endotracheal intubation. In unconscious patients, upper airway problems can usually be resolved by inserting an oral airway and positioning the patients on their sides with pillows and sandbags. Premature endotracheal intubation or tracheostomy is dangerous if there is inadequate supervision to ensure frequent suction and adequate humidification. Changes in pCO_2 resulting from over- or under-ventilation can affect cerebral blood flow and intracranial pressure. Conversely, prompt intubation and mechanical ventilation, when available, may be life-saving in patients with acute respiratory distress syndrome, aspiration pneumonia or neurogenic respiratory arrest. Attempts at intubation by inexperienced personnel may lead to periods of carbon dioxide retention, with consequent raised intracranial pressure. Once mechanical ventilation has been instituted, pCO_2 should be maintained below 4·0.

Misdiagnosis of respiratory distress. In patients with severe malaria, 4 serious complications—pulmonary oedema, acute respiratory distress syndrome, aspiration pneumonia and metabolic acidosis—may be confused clinically. Measurement of central venous pressure and even pulmonary arterial wedge pressure may not always distinguish between them, but a chest radiograph is helpful (WARRELL & WHITE, 1984).

Failure to control convulsions. Convulsions are dangerous and should be prevented or treated promptly with appropriate drugs. Aspiration pneumonia during convulsions must be prevented by laying the patient on his/her side and, in cases of repeated seizures, inserting a cuffed endotracheal tube,.

Failure to recognize and treat severe anaemia. Severe anaemia may cause, or contribute to, death in severe malaria. Ideally, haematocrit should be measured twice a day and provision for blood transfusion must be made when the degree of anaemia becomes intolerable. This will often be associated with a haematocrit falling below 15% (but see pp. S1/10, S1/14, S1/44, S1/49–S1/52). In children, breathlessness (respiratory distress) may be misinterpreted as 'anaemic heart failure' when urgent correction of hypovolaemia is required.

Use of inappropriate and potentially dangerous ancillary therapies. There have been many fashionable ancillary therapies advocated for severe malaria. The following are potentially dangerous and of **no** proved benefit: corticosteroids, anti-inflammatory agents, osmotic agents, dextran, heparin, adrenaline, prostacyclin, cyclosporin A desferrioxamine B (WARRELL, 1999).

Delay in starting peritoneal dialysis. Failure to use peritoneal dialysis (if available) early for established renal failure. This may have to be continued for several weeks. Do not give up too early. Cloudy effluent dialysate must be examined under the microscope for cells as an early sign of peritonitis, which is a very common complication of peritoneal dialysis in the tropics.

ANNEX 1
Pharmacology of antimalarial drugs in severe falciparum malaria

Severe malaria is a medical emergency requiring immediate administration of rapidly effective antimalarial drugs. When possible, drugs should be given intravenously, but studies to date suggest adequate absorption of quinine, artesunate, and chloroquine after intramuscular (and in the case of chloroquine subcutaneous) injections, and these are acceptable alternatives. Parenteral artemether is given only by intramuscular injection. Suppository formulations of chloroquine, artemisinin, and artesunate are available in some countries but more pharmacokinetic data are needed and quinine and Quinimax® have been administered intrarectally. Although parenteral treatment is needed in the acute stage, oral treatment should be substituted as soon as the patient is able to take fluids by mouth. If it is not possible to give parenteral treatment, treatment by mouth or via nasogastric tube should be started immediately as drug absorption appears to be adequate even in severe malaria, but this route of administration cannot be relied upon. Adequate pharma-cokinetic data in severe malaria now exist for the quinoline antimalarial drugs (WHITE, 1985) but, despite extensive use in south-east Asia over the past decade, there is still a paucity of data on the pharmacokinetic properties of the artemisinin derivatives.

General considerations

Antimalarial pharmacodynamics. The objective of antimalarial treatment in severe malaria is to inhibit the development of, or kill, a sufficient number of parasites to prevent death. The pharmacodynamic properties of the antimalarial drugs can be described in terms of the stage specificity of their antiparasitic action during the asexual life cycle and both the concentration–effect relationship and their maximal effect. These can be determined *in vitro*, but this is of uncertain relevance to effects *in vivo*. Activity *in vivo* is best described by the kinetics of the decline in parasitaemia after drug treatment, although it cannot be assumed that this will correlate with life-saving efficacy in severe malaria. In the past this has been measured as parasite clearance times, but as the process is first-order, and therefore related to initial parasite burden, it is better described as a rate or the fractional reduction in parasitaemia per asexual life cycle, or parasite reduction ratio (WHITE, 1997), Stage specificity refers to the relative sensitivity of the different stages of the asexual parasites' life cycle. For example, the very young rings and the fully mature schizonts appear to be relatively resistant to all the antimalarial drugs (TER KUILE *et al.*, 1993a). Although there is still much to be learned about the rapidity of parasite killing and stage specificity of antimalarial drugs, current evidence suggests that the artemisinin derivatives have the broadest stage specificity of action and the highest rates of parasite clearance or parasite reduction ratios of all the antimalarial drugs. Chloroquine and halofantrine act earlier in the parasite life cycle than quinine or mefloquine. Relatively slow-acting drugs, such as the antibiotics with antimalarial activity, may not prevent maturation and multiplication of the parasite population for one cycle and should not be used as the sole treatment of severe malaria.

Therapeutic index. The therapeutic index refers to the ratio between the 'therapeutic' or effective dose and the toxic dose of a drug. In general, the artemisinin derivatives have a wide therapeutic index, although fears concerning neurotoxicity have not been resolved adequately, whereas the quinoline antimalarial drugs have a low therapeutic index. Nevertheless, with careful attention to dose, route, rate and frequency of administration, serious adverse effects are very unusual. This class of drug should never be given by intravenous bolus, or 'push', injection. Current methods of assessing the therapeutic response to antimalarial drugs are suitable for uncomplicated malaria, but improved methods are needed in severe malaria where the objective of treatment is to save life, and elimination of the infection is a secondary concern.

Quinine

Quinine is the treatment of choice for severe chloroquine-resistant malaria, although artesunate and artemether are effective alternatives. **Although quinine resistance has increased in areas of south-east Asia and South America, there is still no high-grade resistance in severe malaria that precludes its use.** This may change and efficacy in areas of quinine resistance needs to be monitored closely (PUKRITTAYAKAMEE *et al.*, 1994).

Pharmacokinetic properties. (i) *Absorption*. Quinine sulphate is well absorbed when given by mouth in healthy subjects, and in patients with malaria (WHITE *et al.*, 1987a; SUPANARANOND *et al.*, 1991; PAINTAUD *et al.*, 1993). Peak plasma concentrations are reached in 1–3 h (HALL *et al.*, 1973). Use of intramuscular quinine has been controversial for many years, but later studies (CHONGSUPHAJAISIDDHI *et al.*, 1983; SHANN *et al.*, 1985; WATTANAGOON *et al.*, 1986; MANSOR *et al.*, 1990; WALLER *et al.*, 1990; PASVOL *et al.*, 1991; SHAPIRA *et al.*, 1993; WINSTANLEY *et al.*, 1993) suggested good bioavailability even in very young children (<2 years old) with severe malaria (BOELE VAN HENSBROEK *et al.*, 1996b). Overall, there is good agreement between recent studies in African children with moderately severe to severe falciparum malaria. The overall mean peak plasma quinine concentration after the 20 mg/kg loading dose was 15·6 mg/L (SD=5·2; n=57) (WHITE, 1995). This compares with an overall mean peak quinine concentration after intravenous administration of 15·2 mg/L (SD=3·6; n=74). The peak quinine concentrations after both intravenous and intramuscular quinine administration were normally distributed, allowing prediction of the proportions of patients expected to have values below estimated minimum inhibitory concentrations. Absorption is more rapid if quinine dihydrochloride (usual concentration 300 mg/mL) is diluted 1:2 to 1:5 before injection. The plasma concentration profile after intramuscular administration may be biphasic. Quinine should not be given subcutaneously because this can result in skin necrosis. Few published data are available on the use of suppository formulations of cinchona alkaloids, but quinine gluconate as a cream and the commercial mixture of cinchona alkaloids, Quinimax®, in solution, had estimated rectal bioavailabilities of 36% and 40%, and a mean time to peak concentration of 4·1 h (SD=2·4) and 2·7 h (SD=0·4) respectively in children with moderately severe malaria from Niger. These preparations were reportedly well tolerated (BARENNES *et al.*, 1996a, 1996b).

(ii) *Disposition*. Plasma concentration profiles after intravenous injection of a small dose of quinine can be described by an open two-compartment model. Distribution from the central compartment is rapid; the half-life ($t_{1/2}$) is approximately 2 min in both healthy subjects (WHITE *et al.*, 1983b) and patients with cerebral malaria (DAVIS *et al.*, 1988b). A single-compartment model is adequate to define the disposition of quinine after intravenous infusion. The total apparent volume of distribution (V_{ss}) in healthy adult subjects ranges from 1·5 to 3·5 L/kg (WHITE *et al.*, 1982). This is contracted in malaria proportional to the severity of disease (approximately 1·7 L/kg in uncomplicated falciparum malaria and 1·2 L/kg in cerebral malaria). Plasma concentrations for a given dose are therefore highest in severe malaria. In Kenyan children with severe malaria, estimated mean values of the total apparent volume of distribution were lower: 1·22 L/kg and 0·87 L/kg in severe malaria (PASVOL *et al.*, 1991) and 0·45 L/kg (WINSTANLEY *et al.*, 1993) and 0·75 L/kg (WINSTANLEY *et*

al., 1994) in cerebral malaria. The mean volume of the central compartment (V_1) is also contracted from 0·7 L/kg (SD=0·3) in healthy Thai adults to 0·17 L/kg (SD=0·1) in cerebral malaria (DAVIS *et al.*, 1988b). In Kenyan children with cerebral malaria, the estimated volume of the central compartment was even smaller: 0·27 L/kg (SD=0·1), 40% lower than the value in adults (WINSTANLEY *et al.*, 1993). This explains why intravenous injections of quinine are potentially so dangerous in severe infections. Quinine is distributed throughout most of the body fluids. The mean concentration in erythrocytes is approximately one-third of that in plasma, rising to one-half (presumably because of concentration within malaria parasites) in severe malaria (WHITE *et al.*, 1983c; MANSOR *et al.*, 1990). Concentrations in saliva are one-third of those in plasma (SALAKO & SOWUNMI, 1992). Cerebrospinal fluid concentrations are 7±3% of those in plasma in cerebral malaria (WHITE *et al.*, 1982). These values are approximately half those of free (unbound) quinine in plasma, which suggests that quinine does not freely traverse the blood–brain barrier (SILAMUT *et al.*, 1985). Quinine is a base and the principal plasma protein to which it binds is the acute phase protein, α_1-acid glycoprotein (MIHALY *et al.*, 1987; SILAMUT *et al.*, 1991; WANWIMOLRUK & DENTON, 1992). Plasma protein binding is therefore increased from approximately 85% in healthy subjects to 90–93% in severe malaria (i.e., the free fraction is reduced by one-third to one-half). Thus, although total plasma concentrations are higher in severe malaria, free concentrations may be no different from those in patients with uncomplicated infections or healthy subjects. Increased protein binding may explain why relatively high total plasma quinine concentrations (10–20 mg/L) do not cause major toxicity in the treatment of severe malaria. The relationship between quinine binding (expressed as the association constant) and pH is hyperbolic, so that binding falls with pH to a nadir around pH 7 (WINSTANLEY *et al.*, 1993). This might enhance toxicity in acidosis, although the effect is offset by a reduction in octanol partition reflecting increased ionization, which tends to reduce transport across membranes (P. Winstanley & W. Watkins, personal communication). There is no clinical evidence for increased toxicity of quinine in acidosis.

(iii) *Elimination.* In healthy subjects and patients with malaria, quinine is predominantly (80%) eliminated by hepatic biotransformation (WHITE *et al.*, 1982) first to 3- and 2-hydroxyquinine, and then to a series of more polar water-soluble metabolites. Plasma concentrations of 3-hydroxyquinine are approximately one-third to one-fifth of those of the parent compound, with a lower ratio in malaria indicating impairment of hepatic biotransformation. Free 3-hydroxyquinine has approximately 10% of the antimalarial activity of the parent compound but, as it is only 50% protein-bound compared to over 90% protein-binding for quinine, it contributes approximately 5% of antimalarial activity in acute malaria, rising to 10% in convalescence in uncomplicated malaria (NONTPRASERT *et al.*, 1996; PUKRITTAYAKAMEE *et al.*, 1997). In a recent small study of patients with acute renal failure, it was estimated that 3-hydroxyquinine contributed an average of 12%, and up to 23%, of the antimalarial activity of the parent compound (NEWTON *et al.*, 1999). These polar metabolites do not have significant antimalarial effects, whereas the hydroxylated metabolites retain some activity. 3-Hydroxyquinine has approximately 30% of the antimalarial activity of quinine (A. Nontraprasert & N. J. White: unpublished observations). Approximately 20% of the quinine is eliminated by the kidneys, and the remainder by hepatic biotransformation. Total systemic clearance is reduced in uncomplicated malaria, and further reduced in severe malaria (WHITE *et al.*, 1982; WHITE, 1987). Renal clearance and hepatic clearance are reduced in parallel. The observation that plasma quinine concentrations are high in patients with acute renal failure (CANFIELD *et al.*, 1968; DONADIO *et al.*, 1968) probably relates more to the overall severity of disease and the consequent pharmacokinetic changes rather than to a reduction in glomerular filtration rate *per se* (WHITE, 1985). The mean terminal elimination half-life ($t_{1/2}\beta$) in healthy adult subjects is 11 h, compared with 16 h in uncomplicated malaria and 18 h in cerebral malaria. The clearance of quinine is reduced in the elderly (aged 65–74 in this study) and the terminal elimination half-life is prolonged from 11 to 18 h (WANWIMOLRUK *et al.*, 1991). Quinine elimination is more rapid in tobacco smokers (WANWIMOLRUK *et al.*, 1995), although the relevance of this to malaria is uncertain.

(iv) *In children and pregnant women.* Absorption of quinine is similar in adults and children. The total apparent volume of distribution and the volume of the central compartment are smaller in children (SABCHAROEN *et al.*, 1982; GREENBERG *et al.*, 1989; WALLER *et al.*, 1990; PASVOL *et al.*, 1991; SCHAPIRA *et al.*, 1993; WINSTANLEY *et al.*, 1993) and pregnant women (PHILLIPS *et al.*, 1985) than in adults with disease of comparable severity, but elimination is more rapid in both the former groups. Systemic clearance values are therefore similar. Cord blood concentrations and breast milk concentrations are approximately one-third of those in simultaneously sampled maternal plasma (PHILLIPS *et al.*, 1985).

(v) *Areas of uncertainty.* The disposition of quinine in very fat or very thin persons is not known. It has been suggested that there may be a ceiling dose above which quinine should not be given, but there is no evidence to support this. The relationship between plasma concentration and parasiticidal effect in severe malaria is also unclear. The therapeutic range in serious infections is therefore uncertain. A therapeutic range of free quinine concentrations between 0·2 and 2·0 mg/L (corresponding roughly to total plasma concentrations of 2–20 mg/L) has been suggested for parasites in East Africa on the basis of sensitivity testing *in vitro* (WINSTANLEY *et al.*, 1993). However, free quinine concentrations *in vivo* of less than 0·5 mg/L have been associated with suboptimal parasite clearance rates, suggesting that 0·5 mg/L represents a minimum estimate for the minimum parasiticidal concentration of free quinine in the treatment of malaria (WHITE, 1995). Total plasma concentrations between 8 and 20 mg/L in severe malaria, which correspond to free quinine concentrations of approximately 0·8–2 mg/L, are usually safe and effective (WHITE, 1987, 1996a). The therapeutic range has not been defined more precisely and may be lower in areas where the parasite is more sensitive, but this also remains to be proved. The importance of plasma protein and red cell binding in determining therapeutic effect and toxicity has yet to be determined.

(vi) *Toxicity.* Minor adverse reactions are common with quinine therapy, but severe life-threatening toxicity is rare. A characteristic symptom complex known as cinchonism occurs with plasma concentrations over 5 mg/L (POWELL & MCNAMARA, 1966). This consists of tinnitus, high tone deafness (ROCHE *et al.*, 1990), nausea, uneasiness, malaise, and blurring of vision. Vomiting is likely if core temperatures are high. These symptoms of cinchonism are rarely sufficient to warrant stopping treatment.

Severe concentration-related toxicity, including hypotension, myoacardial conduction disturbance, blindness, deafness, and coma, is very unusual with plasma concentrations below 20 mg/L (WHITE, 1985, 1995; PUKRITTAYAKAMEE *et al.*, 1994). Hypoglycaemia is a more commonly encountered problem. Quinine is a potent stimulus for pancreatic insulin secretion (WHITE *et al.*, 1983a) and hyperinsulinaemic hypoglycaemia is particularly likely in pregnant women (LOOAREESUWAN *et al.*, 1985a) or patients who remain severely ill for several days. Intravenous injections may cause acute cardiovascular toxicity, presumably because transiently toxic

blood concentrations occur before adequate distribution (DAVIS *et al.*, 1988b). Postural hypotension is common in acute malaria and is exacerbated by quinine (SUPANANAROND *et al.*, 1991). Thrombocytopenia, Coomb's-positive haemolytic anaemia, haemolytic–uraemic syndrome, and other allergic manifestations are rare in malaria treatment. Intramuscular quinine is certainly painful if concentrated acidic solutions are administered (undiluted quinine dihydrochloride 300 mg/mL has a pH of 2), and in the past these have been associated with sterile abscess formation. Tetanus associated with intramuscular quinine injections is usually fatal (YEN *et al.*, 1994). In animals, toxic concentrations of quinine are oxytocic and induce premature labour. Quinine was once widely used as an abortifacient. This has led to concern over the use of quinine in pregnancy. However, studies of intravenous quinine in severe malaria showed no evidence of an oxytocic effect (LOOAREESUWAN *et al.*, 1985b). Indeed, administration of quinine was associated with a reduction in uterine irritability. Despite an apparently long list of potential adverse effects, quinine is generally well tolerated in the treatment of malaria. There is a clinically relevant interaction between quinine and, especially, quinidine and digoxin. Both cinchona alkaloids increase the serum concentrations of digoxin (WANDELL *et al.*, 1980; DOERING, 1981; WILKERSON, 1981). Quinine clearance is increased by phenobarbitone, rifampicin and smoking, and reduced by cimetidine.

Quinidine

Quinidine is the dextrorotatory dia-stereoisomer of quinine. It may be more effective than quinine in the treatment of chloroquine-resistant falciparum malaria (WHITE *et al.*, 1981), but it is also more toxic.

Pharmacokinetic properties. The pharmacokinetic properties of quinidine have been extensively reviewed, with particular reference to its use in cardiovascular disease (OCHS *et al.*, 1980). Quinidine is cleared more rapidly, with a greater proportion of renal clearance, than quinine and the total apparent volume of distribution is larger. Elimination half-times are shorter (WHITE *et al.*, 1981). Plasma concentrations of quinidine are therefore lower than those after equivalent doses of quinine. Many of these differences can be explained by the increased free fraction in plasma (KARBWANG *et al.*, 1993); free concentrations are approximately twice those of quinine. Although there is less information, quinidine pharmacokinetic properties are affected in a similar manner to those of quinine in malaria—i.e., clearance and volume of distribution are reduced (WHITE *et al.*, 1981). In adults with severe malaria, the estimated total apparent volume of distribution averaged 1·71 L/kg and total systemic clearance was 1·8 L/h (PHILLIPS *et al.*, 1985). Renal clearance accounted for approximately 40% of total clearance (compared to 20% for quinine). The terminal elimination half-life in severe malaria was 12·8 h. The therapeutic range for total plasma quinidine concentrations is estimated to be approximately 5–8 mg/L (MILLER, K. D. *et al.*, 1989a), corresponding to free concentrations of approximately 0·8– 2 mg/L (WHITE, 1996a). There are no data on intramuscular quinidine in malaria.

Toxicity. Minor toxicity with the 2 dia-stereoisomers is similar, although quinidine has a greater tendency to produce diarrhoea and has much less effect on hearing than quinine (KARBWANG *et al.*, 1993). Quinidine has a four-fold greater effect in prolonging the electrocardiographic QTc interval and has a greater propensity to produce hypotension (WHITE *et al.*, 1983c; PHILLIPS *et al.*, 1985). Electrocardiographic monitoring and close attention to circulatory status are therefore essential when parenteral quinidine is given for the treatment of severe malaria (MILLER, K. D. *et al.*, 1989a). Quinidine is also equally likely to induce hypoglycaemia (PHILLIPS *et al.*, 1986b). Idiosyncratic and allergic reactions are not common. There are even fewer data for quinidine than quinine on which to base a recommended therapeutic range.

Artemisinin and its derivatives

The family of trioxane compounds derived from the plant *Artemisia annua* (qinghaosu) and a series of synthetic derivatives are among the most potent antimalarial compounds known. The trioxane structure contains a peroxide grouping that is essential for antimalarial activity. These naturally occurring sesquiterpene lactones are structurally unrelated to the quinoline antimalarial drugs (KLAYMAN, 1985). Qinghaosu and related compounds were tested extensively in China (QINGHAOSU ANTIMALARIAL CO-ORDINATING GROUP, 1979), and more recently these drugs have been introduced in some parts of south-east Asia and South America to combat multidrug-resistant falciparum malaria. Their rapidity of effect combined with lack of adverse effects has led to widespread availability in the market-place, a matter of concern in areas where they are not needed. Three compounds have been evaluated extensively: the parent compound artemisinin, the water soluble artesunate and the oil-soluble ether artemether. These 2 derivatives are converted to a common biologically active metabolite, dihydroartemisinin, which is 2–3 times more active. Dihydroartemisinin has recently been formulated in China as tablets for oral use and as suppositories. Satisfactory analytical methods for these compounds have been devised only recently. This has hindered studies of their clinical pharmacology. Although HPLC methods with ultraviolet detection of a derivative have given satisfactory results for artemisinin, the more difficult technique of electrochemical detection is required for the other available compounds.

In recent years there has been a number of pharmacokinetic studies conducted using reliable and reproducible assays. These indicate that artesunate is hydrolysed very rapidly to dihydroartemisinin with a half-life of minutes, even in severe malaria. Following oral administration, relatively little unchanged artesunate is detectable. Thus nearly all the antimalarial activity of artesunate is accounted for by its principal metabolite dihydroartemisinin. Artemether is biotransformed more slowly, but following oral administration concentrations of dihydroartemisinin are still higher than those of the parent compound and this contributes the majority of antimalarial activity. Following intramuscular administration, concentrations of the parent drug predominate because first-pass biotransformation is bypassed. Oral artemisinin is well absorbed, but it is not metabolized to other biologically active compounds. Artemisinin, but not the other derivatives, shows considerable autoinduction of its own metabolism so that blood concentrations after several days of dosing are considerably lower than would be predicted from the initial dose (ASHTON *et al.*, 1998). Artemisinin and its derivatives are all rapidly eliminated, yet they have been shown to be equally effective whether given once, twice, or 3 times daily. This challenges the conventional wisdom that blood concentrations must exceed a putative minimum inhibitory concentration throughout the dosing interval (WHITE, 1997), and suggests that pharmacodynamic factors may be more important determinants of the therapeutic response. The artemisinin derivatives give faster parasite clearance and, in most studies, faster fever clearance than other antimalarial drugs (HIEN & WHITE, 1993), they have a broader stage-specificity of action (TER KUILE *et al.*, 1993a), they are very well tolerated, and there is no documented resistance. The only cloud on the horizon is neurotoxicity; in all animal species studied to date, parenteral arteether and artemether have induced an unusual selective pattern of damage to brain stem nuclei. The oral artemisinin derivatives and the water-soluble artesunate are considerably less neurotoxic than the oil-

soluble compounds (NONTPRASERT *et al.*, 1998; T. G. Brewer, personal comm-unication). There is no evidence that this occurs in humans, but it remains a cause for concern (see below). There has been considerable interest in the possibility that these drugs might be better than the quinoline antimalarials for the treatment of severe malaria. The results of 3 large trials have now been published and the meta-analysis is in progress, comparing artemether and quinine in severe falciparum malaria (BOELE VAN HENSBROEK *et al.*, 1996a; MURPHY *et al.*, 1995; TRAN *et al.*, 1996). Artesunate is the most widely used of the compounds, and may be the most rapidly acting. WHO has supported the development of arteether, a compound almost identical to artemether (differing only in the substitution of the methyl group by an ethyl group), which has only recently entered clinical trials. Although the drugs developed originally in China have been used clinically for approximately 20 years, there is still no consensus on which compound should be used or developed for general use in severe malaria.

Artesunate

This is the sodium succinyl salt of dihydroartemisinin. It is water-soluble but unstable in solution at neutral pH, hydrolysing rapidly to the less soluble dihydroartemisinin. It is currently dispensed as dry artesunic acid, which is made up for injection with 5% sodium bicarbonate solution.

Pharmacokinetics. Artesunate is cleared very rapidly after intravenous injection, by conversion to dihydroartemisinin (YANG *et al.*, 1985) with a half-life of approximately 2 min. The biologically active metabolite then declines biexponentially with a terminal half-life of approximately 48 min. After oral administration, very little artesunate is absorbed unchanged; nearly all is hydrolysed to dihydroartemisinin. Absorption is rapid. Recent bioavailability studies indicated 60–70% oral bioavailability (BATTY *et al.*, 1998; P. Teja-Isvadharm, personal communication).

Artemisinin

ASHTON *et al.* (1998) have recently studied the pharmacokinetics of oral and rectal artemisinin in the treatment of uncomplicated malaria. Rectal bioavailability was 30% of that following oral administration, peak concentrations following oral administration averaged approximately 700 ng/mL and were reached in a median of 2·5 h. The mean elimination half-life was 2 h (SD=0·5). The area under the plasma concentration–time curve (AUC) on day 5 was less than 25% of that on the first day, indicating considerable autoinduction. Population studies in children and adults indicated that bioavailability decreased by a factor of 6·9 over the 5 d period (SIDHU *et al.*, 1998). Food did not alter artemisinin pharmacokinetics (DIEN *et al.*, 1997). DE VRIES *et al.* (1997) studied 11 Vietnamese patients with uncomplicated malaria who received a single 500 mg oral dose of artemisinin and reported a mean absorption time of 1·2 h, a maximum concentration of 364 μg/L at 2·9 h after drug intake, and an elimination half-life of 2·7 h.

Artemether

Artemether is an oil-soluble methyl ether formulation for intramuscular injection. It is more stable than artesunate. There is insufficient information to quote accurate pharmacokinetic data for humans, although available studies suggest a considerably longer terminal elimination half-life than artesunate (7–13 h) and less conversion (30%) to dihydroartemisinin (ZHAO *et al.*, 1988; ZHAO, 1988). Dihydroartemisinin levels were considerably lower than those of the parent compound. After oral administration there is a considerable first-pass effect; plasma concentrations of dihydroartemisinin were 3 times higher than those of the parent compound (NA-BANGCHANG *et al.*, 1994). There was no difference in pharmacokinetics between healthy volunteers and patients with uncomplicated malaria. Nearly all antimalarial activity can be accounted for by the combination of artemether and its main metabolite dihydroartemisinin. In volunteers, intramuscular administration had a bioavailability of approximately 25%, and rectal administration approximately 35%, of that of the orally administered drug (TEJA-ISAVADHARM *et al.*, 1996).

In 26 Kenyan children with cerebral malaria, intramuscular injection of artemether (3·2 mg/kg) achieved therapeutic levels in the plasma within one hour in most cases. However, there was marked individual variation and no detectable antimalarial activity in 5 'non-absorbers' (MURPHY *et al.*, 1997). These results should lead to some caution in the use of intramuscular artemether in sick children, especially those with respiratory distress in whom plasma levels were consistently lower than in those without this complication.

Metabolism. Recent studies indicate that artesunate hydrolyses readily at neutral pH, although this may be accelerated by esterases in the blood. Artemether and arteether are biotransformed via cytochrome P450 3A4 predominantly, but then dihydroartemisinin is metabolized principally by conjugation to biologically inactive glucuronides.

Toxicity. Plant extracts (qinghaosu), artesunate and artemether have undergone extensive clinical trials in China, Viet Nam, Thailand and Myanmar in both uncomplicated and severe falciparum malaria. They are rapidly effective and all compounds have been remarkably well tolerated. In particular, there is no acute cardiovascular or other vital organ toxicity. The only adverse effects attributable to the drugs have been fever in some volunteers and a clinically unimportant temporary suppression of reticulocyte count. In animals, high doses cause fetal resorption, erythropoeitic suppression, gastrointestinal toxicity, and—of most concern—neurotoxicity (BREWER *et al.*, 1994a, 1994b). A selective pattern of damage to brain stem nuclei has been observed in all animal species tested. Parenteral doses of artemether and arteether as low as 16 mg/kg/d for 2 weeks have induced these lesions. This represents a total dose 10–20 times larger than currently used. Current studies are attempting to define a 'no-effect' threshold and to determine whether the lesions are reversible, whether there are any early clinical correlates, and whether the water-soluble compounds carry the same risk. The clinical implications of these observations are unclear. There is no evidence to date of any neurotoxicity in humans.

Chloroquine

Chloroquine is the most important of the 4-aminoquinoline compounds. It remains an effective treatment for severe malaria in those few areas where *P. falciparum* retains full sensitivity (North Africa, Central America north of the Panama canal, Haiti, parts of the Middle East and east Asia) (SALAKO & ADEROUNMU, 1987; SIMON *et al.*, 1987; WHITE *et al.*, 1987b, 1988b).

Pharmacokinetics. (i) *Absorption.* Chloroquine is rapidly absorbed after oral administration in healthy adults (GUSTAFSSON *et al.*, 1983) and children with uncomplicated malaria (ADELUSI *et al.*, 1982). In adults with malaria of moderate severity, acute bioavailability relative to parenteral treatment was 70% (WHITE *et al.*, 1987b) compared with 75% in healthy adults (GUSTAFSSON *et al.*, 1983). In children with uncomplicated malaria given an initial treatment dose of 10 mg base/kg as tablets, peak plasma concentrations of approximately 250 μg/L were reached in 2 h (ADELUSI *et al.*, 1982). In 8 children with severe malaria given chloroquine syrup by nasogastric tube (initial dose, 10 mg/kg of **base** followed by 5 mg/kg of **base** at 6, 24 and 48 h), whole blood concentrations reached an average of 600 μg/L

within 4 h (WHITE *et al.*, 1988b). Intramuscular and subcutaneous routes of administration of chloroquine give almost identical plasma or whole blood concentration profiles. Absorption is very rapid and relatively complete even in very severe infections (WHITE *et al.*, 1987b, 1988b). Time to peak concentration (t_{max}) in severe malaria is usually 20 min and can be as short as 5 min. This results in transiently high (500–3500 μg/L) and potentially toxic blood concentrations if doses of 5 mg/kg **base** or more are given (WHITE *et al.*, 1988b). Formulations which slightly retard the rate of absorption after intramuscular or subcutaneous administration would presumably have a wider safety margin (PRAKONGPAN *et al.*, 1989). Chloroquine administered as rectal suppositories has a bioavailability of approximately 30–50%, and a rate of absorption similar to that of oral chloroquine in healthy volunteers (MINKER & IVAN, 1991).

(ii) *Distribution*. The pharmacokinetic properties of chloroquine are complex. The total apparent volume of distribution is enormous (100–1000 L/kg) because of extensive tissue binding (FRISK-HOLMBERG *et al.*, 1984), whereas the volume of the central compartment is several orders of magnitude smaller: 0·18 L/kg (SD=0·13) (LOOAREESUWAN *et al.*, 1986). The processes of distribution out from this central compartment determine the blood concentration profile during the treatment of malaria.

There is a multiexponential decline in blood concentration following a single dose. By ignoring the long terminal elimination phase, this can be simplified into a simple two-compartment model in order to characterize the blood concentration profile during therapy and predict levels following alternative regimens (WHITE *et al.*, 1988b). The profile of blood concentration after parenteral administration is characterized by sharp peaks with wide peak-to-trough variation. Even 4 h infusions of 5 mg/kg **base** is insufficient to allow adequate distribution out from the central compartment, and so constant rate continuous infusion is the simplest method of avoiding potentially toxic peak concentrations. For intramuscular and subcutaneous administration, small frequent doses (e.g., 3·5 mg/kg **base** every 6 h or 2·5 mg/kg **base** every 4 h) are preferable for the same reason (WHITE *et al.*, 1987b) and have been shown recently to avoid transient hypotension associated with the conventional regimen of 5 mg/kg **base** every 12 h (WHITE *et al.*, 1988b).

Chloroquine concentrations in red blood cells are approximately 3 times higher than in plasma, and there is considerable concentration in granulocytes and platelets. Whole blood concentrations are 6–10 times higher than plasma concentrations (GUSTAFSSON *et al.*, 1983). As a consequence, chloroquine concentrations in serum or plasma samples contaminated by these blood elements are variably higher than in carefully and gently centrifuged plasma samples (BERGQVIST & DOMEIJ-NYBERG, 1983). In samples centrifuged at 3000 ***g*** or more, damage to platelets and leucocytes may release the drug. For measurement, whole blood is preferable in field situations where the feasibility of suitable centrifugation is limited or does not exist.

The enormous apparent volume of distribution results from considerable binding in organs such as the liver, connective tissue and tissues containing melanin such as the skin and retina. Chloroquine is 55% protein-bound in plasma (ADELUSI & SALAKO, 1982; WALKER *et al.*, 1983). Concentrations in the cerebrospinal fluid are very low, with a mean value of 2·7% of the corresponding whole blood concentration (WHITE *et al.*, 19888b). Chloroquine is concentrated slightly in breast milk with area under the concentration–time curve milk:plasma ratios of 2·0–4·3 (EDSTEIN *et al.*, 1986).

(iii) *Elimination*. Chloroquine is 51% cleared unchanged by the kidney (GUSTAFSSON *et al.*, 1983). The remainder is biotransformed by the liver, mainly to desethyl- and bidose-chloroquine. Elimination is reduced in renal failure but this is irrelevant in acute malaria (i.e., dosage need not be changed) (SALAKO *et al.*, 1984). The principal metabolite, desethylchloroquine, is less active than the parent compound against *P. falciparum* and is also eliminated more slowly (GUSTAFSSON *et al.*, 1987). Although this metabolite contributes towards prophylactic efficacy, its concentration is not relevant to the treatment of severe malaria. The terminal elimination half-life ($t_{1/2}\beta$) is approximately 1–2 months but, in terms of curative treatment (blood concentration), the real half-life ($t_{1/2}$) is about 6–10 d (FRISK-HOLMBERG *et al.*, 1984). Racemic chloroquine consists of R and S enantiomers. In a recent cross-over study, the mean terminal elimination half-life of R enantiomer (estimated at 294 h) was longer than that of the S enantiomer (236 h) (AUGUSTINS & VERBEKE, 1993). Overall, hydroxychloroquine has approximately similar pharmacokinetic properties to chloroquine (TETT *et al.*, 1988).

Children and pregnant women. The absorption and disposition of chloroquine in children appears to be similar to that in adults (WHITE *et al.*, 1988b). There is no study of chloroquine pharmacokinetics in the treatment of malaria in pregnancy.

Toxicity. Chloroquine is one of the most widely used drugs in the world. It still accounts for over 90% by weight of the global antimalarial drug consumption. It has undoubtedly saved many patients with severe malaria. Much of the reported toxicity at therapeutic doses is anecdotal and poorly documented.

Acute toxicity. Oral chloroquine is usually well tolerated. Nausea, headache, uneasiness and dysphoria are relatively common but seldom serious. Patients may vomit and may complain of blurred vision. Postural hypotension associated with malaria may be exacerbated and pruritus can be severe especially, though not exclusively, in dark-skinned patients. In Nigeria the incidence of pruritus was 14% with chloroquine, 27% with amodiaquine, 13% with halofantrine, and zero with quinine and mefloquine (SOWUNMI *et al.*, 1989). Pruritus responds to steroids and niacin but not to antihistamines (ABILA & IKUEZE, 1989; AJAYI *et al.*, 1991). Parenteral chloroquine is a potent vasodilator. Hypotension is a predictable consequence of the transiently high blood concentrations that follow parenteral administration (LOOAREESUWAN *et al.*, 1986; WHITE *et al.*, 1988b).

There are several reports of sudden death following administration of intramuscular chloroquine to children with severe malaria (HARRIS, 1955; TUBOKU-METZGER, 1964; WILLIAMS, 1966; OLATUNDE, 1970). These probably resulted from cardiovascular toxicity. Fatal hypotension would be most likely if severely ill, febrile, dehydrated children were inadvertently given a large intramuscular dose (i.e., without adjusting for weight or surface area) or if the injection was given intravenously by mistake and the child was then nursed upright (WHITE *et al.*, 1987b). This potentially lethal toxicity can be circumvented by giving continuous constant-rate intravenous infusions, or giving smaller, more frequent intramuscular or subcutaneous doses than previously recommended (WHITE *et al.*, 1988b). Chloroquine overdose (usually self-poisoning) is manifested by coma, convulsions, dysrhythmias and hypotension. Diazepam is a specific antidote (RIOU *et al.*, 1988). Oral activated charcoal should be given. Intensive care management is required. Acute neuropsychiatric psychosis (BHATIA *et al.*, 1988), dyskinesias, tremor, cerebellar toxicity, hearing loss, or allergic reactions to chloroquine are rare. In prophylaxis they have been estimated to occur in 0·01% of chloroquine recipients (LOBEL *et al.*, 1993; STEFFEN *et al.*, 1993). One study suggested that ampicillin bioavailability in healthy subjects was significantly reduced by co-administration of chloroquine (ALI, 1985).

Chronic toxicity. Administration of more than 100 g of chloroquine (i.e., weekly prophylactic use for more than 5 years) to adults is associated with an increased risk of retinopathy, but this appears to be associated mainly with the higher doses used in coallagen–vascular diseases (EASTERBROOK, 1988; AYLWARD, 1993; LANGE *et al.*, 1994). All subjects on long-term chloroquine prophylaxis should have regular ophthalmological assessment.

Skeletal and cardiac myopathy may occur in patients receiving high-dose chloroquine maintenance therapy for rheumatoid arthritis. A few reports suggest that chloroquine can aggravate psoriasis, particularly in patients with light-intolerant disease (BAKER, 1966; OLSEN, 1981).

Amodiaquine

Amodiaquine is at least as effective as chloroquine against chloroquine-sensitive *P. falciparum*. Parasites with RI, RII, and even RIII resistance to chloroquine may retain sensitivity, or be less resistant, to amodiaquine (WATKINS *et al.*, 1984; LOOAREESUWAN *et al.*, 1985b; NEVILL *et al.*, 1994), although this is not universal (WATT *et al.*, 1987). Amodiaquine may be a useful substitute for chloroquine when oral treatment is required (OLLIARO *et al.*, 1996). A parenteral formulation of amodiaquine is not commercially available, but the closely related compound amopyraquine is available for intramuscular injection in many francophone countries in Africa. Concern that amodiaquine causes a high prevalence of agranulocytosis (HATTON *et al.*, 1986) and hepatitis (NEFTEL *et al.*, 1986) has terminated its prophylactic use. Serious toxicity has not been reported when amodiaquine has been employed for acute malaria, and this may be partly explained by disease-induced changes in the disposition of the drug (WINSTANLEY *et al.*, 1987). Amodiaquine is rapidly and extensively converted to a pharmacologically active metabolite, desethylamodiaquine, following oral administration, and it seems that this metabolite is responsible for most of the antimalarial activity (CHURCHILL *et al.*, 1985; WINSTANLEY *et al.*, 1987). However, amodiaquine seems to be an unstable molecule and undergoes auto-oxidation in aqueous solution to yield a quinoneimine, which may be implicated in the drug's toxicity (MAGGS *et al.*, 1987, 1988; CHRISTIE & PARK, 1988). Following intravenous administration, the fall in blood amodiaquine concentration is biphasic. The terminal elimination half-life is approximately 10 h, indicating rapid biotransformation to the active metabolite. Mean total volume of distribution was 17·4 L/kg and systemic clearance 5·5 L/kg/h (WHITE *et al.*, 1987c). The pharmacokinetics of intramuscular amopyroquine have been studied by VERDIER *et al.* (1989).

Mefloquine

Mefloquine is a quinoline–methanol compound which structurally resembles quinine. It is effective against all malaria species including multidrug-resistant *P. falciparum*, although significant resistance has developed in south-east Asia. There is no parenteral formulation. Mefloquine has no place in the management of severe malaria.

Absorption. Currently available formulations of mefloquine are well absorbed in healthy subjects and patients with uncomplicated falciparum malaria (KARBWANG *et al.*, 1987a, 1987b; LOOAREESUWAN *et al.*, 1987b; SCHWARTZ *et al.*, 1987; KARBWANG & WHITE, 1990). Absolute bioavailability is not known because there is no parenteral formulation. The absorption profile in malaria appears to be biphasic (KARBWANG *et al.*, 1987a), but with the treatment dose of 15 mg/kg plasma or whole blood concentrations exceeding 500 ng/mL are usually reached within 6 h. Mefloquine suspensions are absorbed slightly better than tablets (DESJARDINS *et al.*, 1979; LOOAREESUWAN *et al.*, 1987c). Absorption may be dose-limited as blood levels are twice as high following a 25 mg/kg dose if the dose is divided compared with single dose administration (TER KUILE *et al.*, 1993b). Mefloquine suspension (mean dose 15·6 mg/kg **base**) has been administered via a nasogastric tube to patients with cerebral malaria who were also receiving quinine (CHANTHAVANICH *et al.*, 1985).

Absorption was rapid, but post-absorption plasma concentrations were 2–3 times lower than in studies in healthy subjects or in uncomplicated malaria, suggesting reduced bioavailability. Recent studies confirm that the bioavailability of mefloquine when given acutely in uncomplicated falciparum malaria is reduced. It is improved considerably when used in combination with artesunate or artemether by delaying the administration of the first dose to the second day of treatment (PRICE *et al.*, 1999). Although in healthy volunteers co-administration of food has increased bioavailability (CREVOISIER *et al.*, 1997), this was not confirmed in acute malaria (PRICE *et al.*, 1999).

Disposition. Mefloquine has a large total apparent volume of distribution (V_f) of 204 L/kg (DESJARDINS *et al.*, 1979; KARBWANG *et al.*, 1987a; SCHWARTZ *et al.*, 1987a). Although the total apparent volume of distribution is probably smaller in acute malaria, changes in the volume of distribution (V_d) cannot be dissociated from changes in the fraction of orally administered drug absorbed (f). In some assays, mefloquine concentrations in red blood cells have been higher than those in plasma (SCHWARTZ *et al.*, 1982; TER KUILE *et al.*, 1994), whereas in others both concentrations have been similar (KARBWANG *et al.*, 1987b). Mefloquine is highly bound (98%) to plasma proteins. Cerebrospinal fluid concentrations are unmeasurable (<5 ng/mL) (CHANTHAVANICH *et al.*, 1985).

Elimination. Mefloquine exhibits a multi-exponential decline in blood concentrations with a terminal elimination half-life of approximately 3 weeks in healthy subjects and 2 weeks in patients with uncomplicated malaria (KARBWANG & WHITE, 1990). Clearance is by hepatic biotransformation. There is enterohepatic recycling of mefloquine in experimental animals. This may be relevant to drug elimination and therefore to steady state concentrations with prophylactic use, and also to diarrhoea—which breaks the enterohepatic cycle, leading to reduced blood concentrations and an increased incidence of treatment failure (TER KUILE *et al.*, 1995).

Toxicity. Mefloquine is generally well tolerated, although nausea, abdominal discomfort, and vertigo occur in 10–20% of patients. Sinus arrhythmia and sinus bradycardia have been noted in several reports but their significance is unclear. Postural hypotension also occurs. There has been concern that mefloquine and quinine in combination may be cardiotoxic, but there is no evidence for this (SUPANARANOND *et al.*, 1997). If patients develop severe malaria following mefloquine treatment a full loading dose of quinine should be given, as the most likely explanation is inadequate mefloquine absorption. If a treatment dose of mefloquine has been taken in the 12 h before severe malaria treatment starts, electrocardiographic monitoring would be advisable if quinine is used. Acute psychosis or transient encephalopathy with convulsions are serious and occur in 0·1% of patients in south-east Asia, but in up to 1% of Caucasian and African patients (PHILLIPS-HOWARD & TER KUILE, 1995). The pathological mechanism underlying neurotoxicity is not understood.

Halofantrine

Halofantrine is a phenanthrene–methanol compound (WATKINS *et al.*, 1988b; WIRIMA *et al.*, 1988). It is more effective than mefloquine against multidrug-resistant falciparum malaria (TER KUILE *et al.*, 1993c). A parenteral formulation has been studied but is not commercially available. The cardiotoxic effects of halofantrine (prolongation of ventricular repolarization) have curtailed its general use.

Halofantrine should not be used in severe malaria. The potential for cardiotoxic interactions between quinine and halofantrine has not been characterized (see below, under Toxicity). Electrocardiographic monitoring should be employed in patients who have received halofantrine and then receive the cinchona alkaloids.

Absorption. The principal problem with current formulations of halofantrine is poor oral bioavailability. It is hoped that a new 'micronized' preparation will reduce the variance in oral bioavailability. Because of erratic and variable absorption, it is currently recommended that the dose of halofantrine be split into 3 parts, with 6 h intervals between doses. Oral bioavailability is increased up to six-fold if halofantrine is taken with a fatty meal (MILTON *et al.*, 1989; SHANKS *et al.*, 1992). Mean values for the time to reach maximum concentration for halofantrine and its principal metabolite desbutylhalofantrine in malaria are 15–16 h and 55–56 h, respectively, with corresponding maximum concentrations (C_{max}) 0·9–1·2 and 0·4–0·5 mg/L, respectively (KARBWANG *et al.*, 1991; VEENENDAAL *et al.*, 1991). Halofantrine absorption is reduced by at least 50% in severe malaria (WATKINS *et al.*, 1995).

Disposition. The estimated apparent volume of distribution is large (100–500 L/kg). Halofantrine is almost entirely eliminated by hepatic biotransformation. The estimated terminal half-life is 3·5–4·5 d (KARBWANG *et al.*, 1991; VEENENDAAL *et al.*, 1991). The principal metabolite, desbutylhalofantrine, has equal biological activity (BASCO *et al.*, 1992), and in malaria has a similar elimination half-life. As plasma concentrations of the metabolite usually exceed those of halofantrine by the third day of treatment, they are obviously an important determinant of antimalarial activity and drug efficacy. Halofantrine is extensively bound to low and high density lipoproteins in serum (CENNI *et al.*, 1995).

Toxicity. Halofantrine is generally well tolerated. Abdominal pain and diarrhoea occur rarely but are usually mild and self-limited. Pruritus occurred in 13% of Nigerians taking the drug (SOWUNMI *et al.*, 1989). Halofantrine has no adverse effect on the central nervous system and is better tolerated than mefloquine (TER KUILE *et al.*, 1993c), but it produces consistent concentration-dependent delays in atrioventricular conduction and ventricular repolarization (NOSTEN *et al.*, 1993). Halofantrine has been associated with sudden death, which has been attributed to lethal ventricular arrhythmias. Halofantrine should not be given to patients with a long electrocardiographic QT interval, to patients taking drugs known to prolong the QT interval (i.e., quinine, quinidine, chloroquine, tricyclic antidepressants, neuroleptics, terfenadine, astemizole), or to those who have received mefloquine within the previous 28 d (WHITE, 1996a; TOUZE *et al.*, 1997). If severe malaria develops after halofantrine treatment, it may be safer to use artesunate or artemether rather than quinine treatment.

Pyronaridine

This naphthyridine derivative was synthesized in China in 1970 (ZHENG *et al.*, 1982). It has structural similarities to mepacrine and amodiaquine but, unlike both these drugs, it is highly active against multidrug-resistant *P. falciparum* (see FU *et al.*, 1986; CHILDS *et al.*, 1988). It has been widely used in China for over 10 years. A parenteral formulation is available in China but has not been used widely, so the data on the use of this drug in severe malaria are limited. Sensitive analytical techniques have been developed recently, but reported pharmacokinetic studies have used relatively insensitive methods of analysis.

Absorption. Oral bioavailability of pyronaridine from tablets and capsules is poor. In comparison with intramuscular administration, the area under the concentration–time curve following an oral dose of 600 mg was 19% (SD=7) compared with 32% (SD=7) (FENG *et al.*, 1987), and the mean maximum whole blood concentration was 128 ng/mL (reached after 14 h) compared with 255 ng/mL (after 4·7 h). By contrast, intramuscular pyronaridine (204 mg) was rapidly absorbed, with a mean peak whole blood concentration of 525 ng/mL at 40 min.

Disposition. The pharmacokinetic properties of intravenously administered pyronaridine have not been reported. The whole blood concentration–time profiles after intramuscular injection fitted a two-compartment open model with estimated values for the volume of the central compartment and the total volume of distribution values of 11·1 and 71·5 L/kg, respectively. Pyronaridine is 3–6 times more concentrated in whole blood than plasma.

Elimination. The estimated terminal elimination half-life in patients with malaria was 63±5 h, although it is possible that a more sensitive assay technique might reveal a longer terminal elimination phase.

Toxicity. Severe side effects are apparently rare. In experimental animals there is less acute cardiovascular toxicity than with chloroquine, but this would still probably preclude rapid intravenous administration. In clinical studies diarrhoea, abdominal pain and vomiting have been reported but are seldom dose-limiting.

Sulfadoxine/pyrimethamine (SP)

This is the most used of a family of drug combinations which antagonize parasite folic acid synthesis. They act by sequential inhibition of dihydropteroate synthetase (sulphonamides and sulphones) and dihydrofolate reductase (pyrimethamine and biguanides). A formulation for intramuscular injection is available.

Absorption. Pyrimethamine and sulfadoxine are both well absorbed. In healthy subjects, peak plasma concentrations are reached in 2–6 h (AHMAD & ROGERS, 1980; WEIDEKAMM *et al.*, 1982). Absorption in uncomplicated malaria is similar to that in healthy subjects (SARIKABHUTI *et al.*, 1988; WINSTANLEY *et al.*, 1992). The intramuscular formulation is also well absorbed in moderately severe malaria (WINSTANLEY *et al.*, 1992), with an estimated bioavailability that was similar overall to the oral formulation. However, on the first day after starting intramuscular treatment (the critical period for the treatment of severe malaria), plasma concentrations were less than half those following oral administration. In severe malaria, when given together with quinine, pyrimethamine absorption was more rapid, but sulfadoxine was less well absorbed than in uncomplicated malaria (NEWTON *et al.*, 1993). However, concentrations of both pyrimethamine and sulfadoxine were within the putative therapeutic range from one to 72 h after infection.

Disposition. The apparent volume of distribution of the relatively lipophilic pyrimethamine is 2–3 L/kg (WEIDEKAMM *et al.*, 1987). This is considerably larger than the distribution volume of the lipophobic sulfadoxine (0·1–0·2 L/kg). Plasma protein binding of both components in healthy subjects is high (pyrimethamine 93%, sulfadoxine 88%). Cerebrospinal fluid concentrations of pyrimethamine are approximately 20% of those in serum (WEISS *et al.*, 1988). Red blood cell concentrations of both drugs are less than half those in plasma.

Elimination. Pyrimethamine is cleared predominantly by hepatic biotransformation. Systemic clearance is approximately 20 mL/kg/h (AHMAD & ROGERS, 1980; WEIDEKAMM *et al.*, 1982, 1987) and the terminal elimination half-life is approximately 90 h. Unlike other sulphonamides, only 5% of sulfadoxine is N-acetylated and eliminated in the urine in this form (WHO, 1984). Biotransformation and clearance is approximately 0·5 mL/kg/h and the terminal elimination half-life is 180 h. Both pyrimethamine and sulfadoxine are excreted in breast milk. The amounts likely to be ingested by a suckling baby are unlikely to be effective in treating or preventing malaria but could cause allergic or idiosyncratic reactions.

Toxicity. Intramuscular administration of sulfadoxine/pyrimethamine is not painful. Oral sulfadoxine/pyrimethamine is very well tolerated. Minor adverse effects are rare. There is now an extensive literature on the toxicity of these combinations, but almost all refers to continuous prophylactic use in prevention, and not the single dose treatment of malaria. Prolonged use of pyrimethamine may provoke folate deficiency in vulnerable subjects (pregnant or malnourished patients). Sulphonamides should not be given directly to neonates because of the risk of kernicterus, but sulphonamide treatment of a lactating woman does not pose a threat to her breast-fed neonate unless there is jaundice, prematurity or G-6PD deficiency. Theoretically, there might be a risk of kernicterus if sulphonamides were administered in late pregnancy, just before delivery. However, there has been no documented case of this complication. Prophylactic use of sulfadoxine/pyrimethamine carried an estimated mortality in Americans of between 1:11 000 and 1:25 000 (MILLER, K. D. *et al.*, 1986). Severe allergic cutaneous reactions are the most common serious adverse reactions.

Agranulocytosis and other blood dyscrasias, hepatitis, pulmonary eosinophilia, and neuropathy have been reported. It is generally considered that the risks of severe adverse reactions in the treatment of malaria are small and do not preclude use of these drugs for the treatment of uncomplicated drug-sensitive infections.

Tetracycline

The tetracyclines are relatively slowly acting antimalarial drugs which are used either as prophylactic or adjunctive drugs. They should not be used alone in severe malaria unless no other antimalarial drug is available. There are extensive reviews of their clinical pharmacology when used as antibacterial drugs. The pharmacokinetic properties of the different tetracyclines vary. There has been no study of the absorption or disposition of tetracyclines in acute malaria. Tetracycline has better oral bioavailability than oxy- or chlor-tetracycline. Plateau concentrations following regular dosing of 250 mg every 6 h range between 2 and 3 μg/mL. Oral bioavailability is increased in the fasting stage, and may be considerably reduced by chelation to divalent cations (e.g., calcium in milk, magnesium and aluminium in antacids, iron preparations). Tetracycline has an elimination half-life of approximately 8 h. Doxycycline has better oral bioavailability than most of the other tetracyclines, a peak concentration of 3·0 μg/mL being reached within 2–3 h. Compared to tetracycline, food interferes less with absorption of doxycycline after an oral dose of 200 mg. The elimination half-life is 18–22 h. All the tetracyclines are excreted by glomerular filtration in the urine (tetracycline 70%, doxycycline 40%, minocycline 5%) and also in the bile. Most of the tetracyclines accumulate in renal failure, but doxycycline, chlortetracycline and probably minocycline do not.

Toxicity. Nausea, heartburn, abdominal pain, vomiting, and diarrhoea are not uncommon. *Candida* superinfections and pseudomembraneous colitis may occur. Hypersensitivity is rare, but photosensitivity is fairly common (particularly with desmethylchlortetracycline). These drugs deposit in calcifying areas of bones and teeth and should not be used in children under 8 years old or in pregnancy. Tetracyclines may cause nephrotoxicity by 5 different mechanisms: they may aggravate pre-existing renal failure by their anti-anabolic effects; they may very rarely cause a hepatorenal syndrome in association with acute fatty liver; outdated degraded tetracyclines may cause tubular damage (Fanconi-like syndrome); desmethylchlortetracycline induces nephrogenic diabetes insipidus; and, on rare occasions, an interstitial nephritis may develop. With the exception of doxycycline, these drugs are contraindicated in renal failure. For these reasons tetracyclines should not be given in the acute phase of severe malaria.

Antimalarial biguanides

There has been a resurgence of interest in these compounds, which were originally developed over 40 years ago. They were the first of the antimalarial dihydrofolate-reductase inhibitors. Two compounds, proguanil and chlorproguanil, are in current use. There is no parenteral formulation; these drugs should not be used in severe malaria. Both are prodrugs for the biologically active triazine metabolites cycloguanil and chlorcycloguanil, respectively. Pharmacokinetic studies have been reported (BYGBJERG *et al.*, 1987; WATKINS *et al.*, 1987; WATTANAGOON *et al.*, 1987). These suggest that the elimination of the parent compounds determines the blood concentration profiles of the active metabolites. For proguanil, estimated elimination half-life values range from 11 to 20 h. Proguanil and the inactive metabolite parachlorphenylbiguanide, but not cycloguanil, are concentrated in red blood cells. Studies in Kenya have shown that the combination of chlorproguanil and dapsone ('lap-dap') is an effective treatment for non-severe falciparum malaria (WATKINS *et al.*, 1988a), but otherwise these drugs are now used exclusively for prophylaxis.

ANNEX 2
Salt–base equivalents of common quinoline antimalarial drugs

Antimalarial drug	Salt (mg)	Base (mg)
Amodiaquine sulphate	130	100
Chloroquine sulphate	136	100
Chloroquine phosphate	161	100
Chloroquine hydrochloride	123	100
Halofantrine hydrochloride	107	100
Mefloquine hydrochloride	110	100
Quinidine gluconate	145	100
Quinidine sulphate	108	100
Quinidine bisulphate	145	100
Quinine dihydrochloride	105	100
Quinine hydrochloride	105	100
Quinine sulphate	103	100

ANNEX 3
Measurement of central venous pressure

The jugular venous pressure is a clinical measure of central venous pressure (Fig. 24). It is the height of the pulsating column of blood in the great veins draining into the right atrium and, in malaria, is a useful measure of over- or under-hydration (hyper- or hypovolaemia).

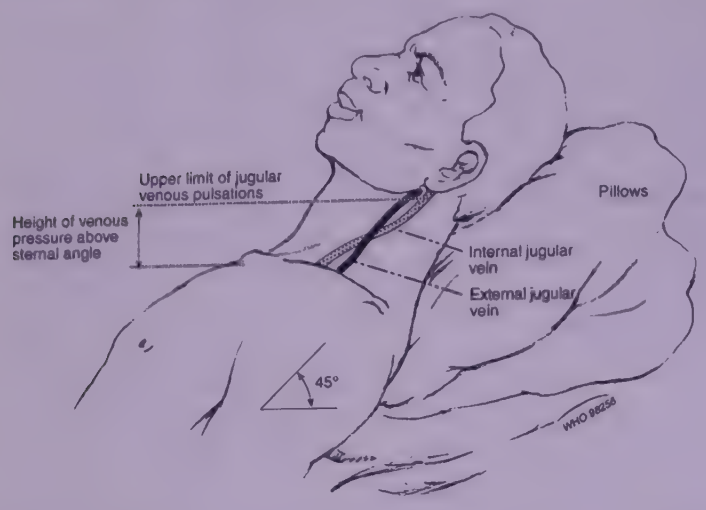

Fig. 24. Measurement of jugular venous pressure in a patient lying in bed with head and shoulders propped up with pillows at an angle of 45°. The jugular venous pressure is the vertical distance beteween the level of the jugular venous pulsation (in the internal jugular vein) and the sternal angle (angle of Louis).

The jugular venous pressure is the vertical distance, measured in centimetres, between the venous pulsation in the neck and the sternal angle (junction of the second rib with the sternum) when the patient is propped up on pillows at 45° to the horizontal. In this position, the sternal angle marks the level of the right atrium. The height of the jugular venous pressure is normally 4–5 cm. In order to measure it, the patient should be made as comfortable and relaxed as possible. It is difficult or impossible to identify venous pulsation if the neck muscles are contracted. Try to achieve good (oblique) lighting of the neck. Look for the jugular venous pulse in the internal jugular vein or its external jugular tributaries on both sides of the neck with the patient's chin tilted up and slightly away from you. The following characteristics help to distinguish jugular venous pulsation from carotid arterial pulsation.

(i) The jugular venous pulse has 2 waves for every single carotid arterial pulsation. Make this comparison by gently palpating the carotid pulse on the opposite side of the neck.

(ii) The height of the jugular venous pressure falls with inspiration and rises with expiration (except when there is cardiac tamponade).

(iii) The jugular venous pulse can be obliterated by pressing firmly but gently with the back of the index finger placed horizontally just above the clavicle at the root of the neck.

(iv) The jugular venous pulse may be visible only when the patient is lying flat (in case of hypovolaemia) or when the patient is sitting upright at 90° (for example in severe congestive cardiac failure).

(v) The jugular venous pulse is usually impalpable.

Do not be misled by what appears to be a high venous pressure but is only a non-pulsatile column of blood trapped in the external jugular vein. To avoid being misled, press firmly but gently just above the clavicle so as to trap blood in the external jugular veins. When the pressure is suddenly released, the engorged veins should collapse immediately unless there is high central venous pressure. The jugular venous pressure cannot be assessed when there is gross tricuspid valve regurgitation.

A useful confirmatory procedure at the bedside is to press firmly but gently on the abdomen (especially over the liver) and observe the rise, and fall after release of pressure, of the jugular venous pressure (hepatojugular reflex).

Assessment of jugular venous pressure in children

In children below 2 years of age, and especially in infants, the jugular venous pressure is virtually impossible to assess by inspection. In children over 2 years old, an attempt can be made to assess the jugular venous pressure as in adults (above), provided the child is relaxed or unconscious. At all ages, liver size and, especially, change in liver size are more useful bedside indicators of central venous pressure.

Measurement of central venous pressure

In seriously ill patients, or those in whom clinical assessment is considered inaccurate, a central venous catheter should be inserted. A catheter may be inserted into the jugular or subclavian vein provided adequate facilities for sterile procedure and subsequent nursing are available. Four approaches are possible: antecubital (Fig. 25), infraclavicular (Fig. 26), supraclavicular (Fig. 27) and internal jugular. A long catheter (at least 50 cm for an adult) is required. The antecubital approach is safest and haemostasis is most easily achieved (by local pressure) and this site. Before readings can be taken, the

Fig. 25. Central venous pressure monitoring in a township hospital in rural Myanmar. A catheter 70 cm long was inserted into an antecubital vein (Seldinger technique) and advanced until its tip was in the superior vena cava. An extension tube was connected to a simple saline manometer with its zero point at the level of the mid-axillary line. (©D. A. Warrell.)

Fig. 26. Central venous pressure monitoring. Puncture of subclavian vein (infraclavicular approach) preparatory to inserting a guide wire and short catheter (Seldinger technique). (©D. A. Warrell.)

Fig. 27. Central venous pressure monitoring. Surface marking of the subclavian vein for needle insertion by the supraclavicular approach. (©D. A. Warrell.)

Fig. 28. Central venous pressure monitoring. Levelling the manometer at the mid-axillary line using a home-made ruler-plus-glass ampoule 'spirit level', in a provincial hospital in Thailand. (©D. A. Warrell).

zero on the manometer must be aligned as accurately as possible with the horizontal plane of the right atrium. A simple 'spirit level' (e.g., a 20 mL glass ampoule, containing an air bubble in water or saline, taped to a ruler) can be used to locate the manometer zero at the same height as an appropriate chest-wall landmark, such as the mid-axillary line, in the supine patient (Fig. 28).

A central venous catheter should be used with strict attention to asepsis. Infection and thrombosis are potential complications, especially if the catheter remains in place for a long time (KAYE & SMITH, 1988).

ANNEX 4
Cannulating the femoral vein

In a shocked adult or child with hypotension and collapsed peripheral veins, the femoral veins may provide the only possibility for venous access.

Anatomy

The femoral vein lies immediately medial to the femoral artery at about the mid-point of the inguinal (Poupart's) ligament at the groin (Fig. 29).

Method

With the patient lying supine with their right thigh slightly abducted and externally rotated, locate the femoral arterial pulse at the groin with the index and middle fingers of your left hand. Clean the skin thoroughly with alcohol or iodine and, with full sterile precautions, mount the cannula (e.g., Abbocath®, Venflon®) with its introducing needle on a syringe. Puncture the skin just medial to the femoral artery, just below the groin crease, and, with the cannula assembly at an angle of 45°, advance gently, aspirating repeatedly until the vein is entered and blood drawn back. If the needle meets firm resistance withdraw, millimetre by millimetre, aspirating each time until blood can be drawn back freely with the syringe. Once you are confident that the needle tip is in the lumen of the vein, flatten the angle slightly and advance the cannula into the vein. Secure the cannula in place with a gauze pad and sticking plaster. Alternatively, the left femoral vein may be cannulated; this is more convenient if the operator is left handed.

Caution: infection and thrombosis of the femoral vein are serious complications. Avoid leaving a femoral cannula in place for longer than is absolutely necessary.

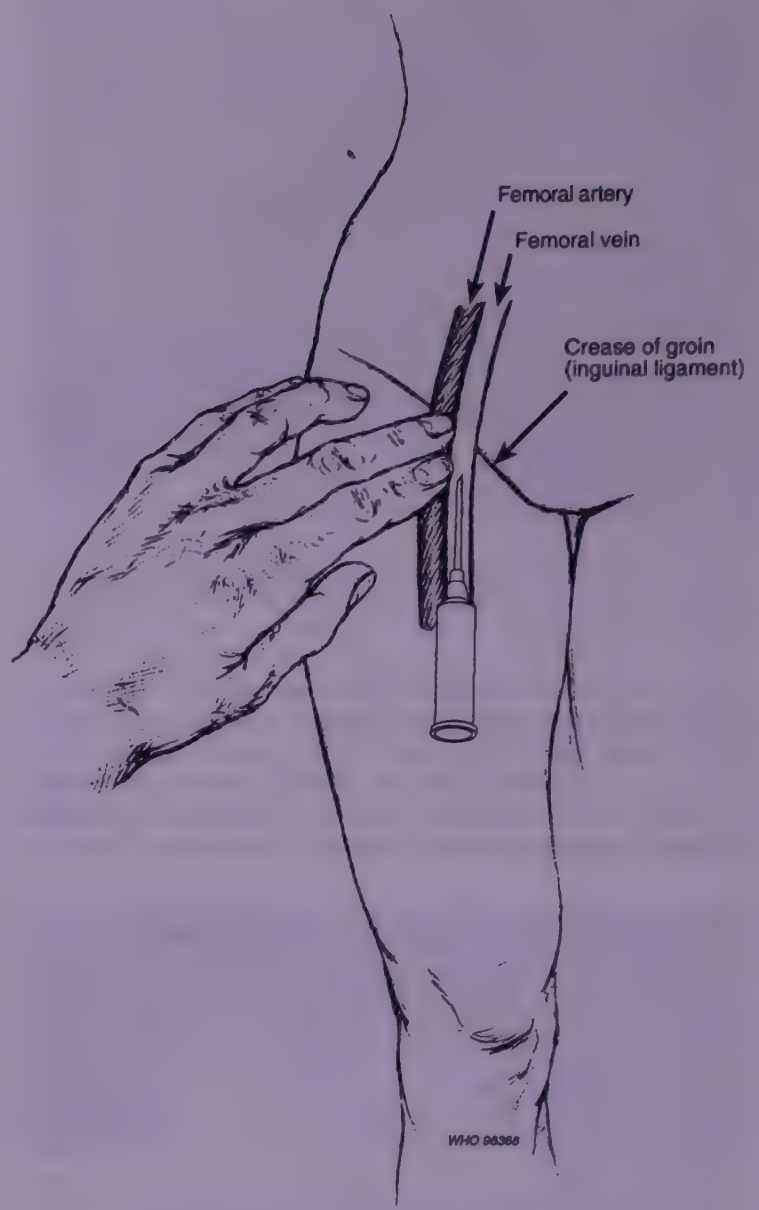

Fig. 29. Location of the femoral arterial pulse and site for insertion of a cannula in the femoral vein.

ANNEX 5
Setting up an intra-osseous infusion in children

If intravenous access is impossible, an intra-osseous infusion can be life-saving. It can be used to administer anything that would normally be given intravenously, i.e., fluids, whole blood, packed cells, or drugs.

Equipment

Alcohol swabs.

A small syringe and fine needle for giving local anaesthetic (unnecessary if patient is comatose).

Local anaesthetic, e.g. 1% lignocaine (=lidocaine).

An 18-gauge needle with trochar (special needles are made for intra-osseous infusion). Alternatively a bone-marrow aspiration needle, or even a standard gauge 17–21 disposable needle, can be used.

Intravenous bottle and drip set, or 50 mL syringe containing fluid for infusion.

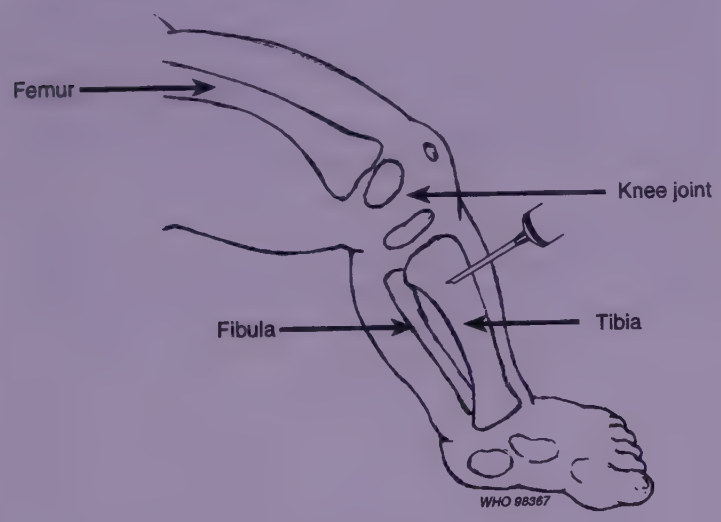

Fig. 30. Site for insertion of an intra-osseous infusion in the tibia of a child.

Procedure (with full sterile precautions)

Choose a point for insertion of the infusion needle in the middle of the wide flat part of the tibia, about 2 cm below the line of the knee joint (Fig. 30). Do not use a site of trauma or skin sepsis.

If the patient is conscious, infiltrate the skin and underlying periosteum with 1% lidocaine.

With the needle vertical to the skin, press firmly with a slight twisting motion until the needle enters the marrow cavity with a sudden 'give'.

Attach a 5 mL syringe and aspirate to confirm that the position is correct. The aspirate can be used for a blood film, blood culture and blood glucose measurement.

The infusion needle should be held in place with sticking plaster (a plaster of Paris cast can be used, as with a scalp vein needle) and the child's mother or minder asked to hold the leg.

Notes

An infusion can be placed in each leg, either simultaneously or in sequence, if necessary.

An alternative site for an intra-osseus infusion is the antero-lateral surface of the femur, 2–3 cm above the lateral condyle.

An infusion allowed to drip through the needle in the usual way (by gravity) may go very slowly. For urgent administration a 50 mL syringe can be used to push in the required fluid in boluses.

Possible complications

Sepsis. An intra-osseous line must not be left in one site for more than 6–8 h; after this time sepsis is increasingly likely to develop.

Compartment syndrome. If the needle is allowed to pass entirely through the tibia, fluid may be infused into the posterior compartment of the leg causing swelling and eventually impairing circulation. Circulation in the distal leg must be checked at regular intervals.

ANNEX 6
Post-mortem needle necropsy of the brain

(For the confirmation of cerebral malaria and other encephalopathies—e.g., rabies, Japanese encephalitis)

If relatives are unwilling to allow full autopsy with opening of the skull, post-mortem needle necropsy of the brain via the superior orbital fissure (WARRELL *et al.*, 1982; TONG *et al.*, 1999), foramen magnum (WARRELL *et al.*, 1982), nostril and ethmoid bone (RANQUE, 1986), or fontanelles (in infants and young children) may be acceptable. The needle puncture holes in the skin or mucosa do not disfigure the cadaver and the superior orbital fissure and trans-ethmoidal approaches leave no mark on the body.

Ideally, a Vim–Silverman needle (Franklin modification) or a comparable metal biopsy needle (including many types of Trucut™ and other liver biopsy needles) at least 9 cm long is used.

Foramen magnum

The neck of the cadaver is flexed and the needle is inserted just below the prominent atlas vertebra in the nape of the neck at the base of the skull and advanced in the direction of the nasion (bridge of the nose), as for cisternal puncture. Cisternal cerebrospinal fluid may be sampled (e.g., for cytology or detection of viral IgM). The needle is then angled against the neck, so that its point is directed upwards towards the foramen magnum, and advanced into the hindbrain.

Superior orbital fissure

The upper eyelid is raised at the inner canthus of the eye and the needle is inserted through the tarsal–bulbar pouch of the conjunctiva, displacing the eyeball downwards and laterally. The needle is advanced perpendicularly alongside the nasal bone until it touches the orbital bone and manipulated up and down and medially until a point is found where there is no bony resistance. The needle is then advanced through the superior orbital fissure. After removing the needle the eyelid and eye are readjusted, leaving no visible blemish.

A core of grey matter (distinguishable macroscopically from white matter) is selected and smeared between 2 glass slides. This can be stained with any Romanowsky method. Under the microscope the slide is scanned for small blood vessels (cerebral capillaries and venules). Endothelial nuclei will be seen and, in cerebral malaria, sequestered parasitized erythrocytes containing schizonts with malaria pigment. Pigment and merozoites may be seen free in the vessels.

ANNEX 7
Peritoneal dialysis procedure

Because of the risk of infection, bleeding, and perforation of abdominal organs, insertion of the catheter should be carried out in an operating theatre.

The incidence of complications is increased in patients with ileus or adhesions from previous abdominal surgery.

The abdomen should be examined carefully to exclude gross hepatomegaly, splenomegaly, renal enlargement and other pathology (e.g., abdominal tumour, aortic aneurism).

Written informed consent must be obtained from patients or their relatives.

Placement procedure

(i) Empty the patient's bladder.

(ii) Put on mask, cap, gown and sterile gloves.

(iii) Clean, prepare and drape the skin overlying the desired insertion site. The preferred site is approximately 5 cm below the umbilicus in the midline. Previous catheter insertion sites or scars should be avoided by at least 3–4 cm.

(iv) Anaesthetize the full depth of the abdominal wall around the desired site with local anaesthetic agent (e.g., 1% lignocaine [=lidocaine]).

(v) Make a 1–2 cm incision over the desired site. Dissect down to the level of the peritoneum with blunt haemostatic forceps. While asking the patient to tense the abdominal wall, insert a small needle with cannula (e.g., 16 gauge intravenous catheter). The needle should be at least 6–8 cm long in order to reach the peritoneal space. Remove the needle, leaving the cannula in place. Infuse 1–2 L of dialysis solution* into the peritoneal cavity until the abdomen becomes moderately tense. Observe the patient carefully for respiratory discomfort.

(vi) Remove the cannula and, in the same location and while the patient again tenses the abdomen, push the stylet-catheter through the abdominal wall aiming 20° off the perpendicular toward the patient's sacrum and advancing approximately 6–8 cm. Remove the stylet while holding the catheter in place. Peritoneal fluid should escape through the catheter.

(vii) Replace the stylet, stopping 1 cm short of full insertion. Aim the stylet and catheter toward the left inguinal ligament, keeping the stylet as flat as possible against the abdominal wall. Advance the catheter without advancing the stylet into the abdominal cavity until the catheter meets firm resistance or the patient experiences tenesmus

(viii) Remove the stylet, connect the catheter to the dialysis tubing and begin draining off fluid. An initial residual volume less than 300 mL is acceptable. If there is no flow, or more than 300 mL are left behind in the peritoneal cavity, withdraw the catheter slightly and adjust the position until a satisfactory outflow is achieved.

(ix) Suture the catheter in place using a purse string suture.

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*For the composition of the dialysis fluid see footnote, p. S1/45.

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